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(54) Title: METHOD OF TREATING HAIR LOSS USING KETOAMIDES

(57) Abstract

The present disclosure describes methods for treating hair loss in mammals, including arresting and/or reversing hair loss and promoting hair growth. The methods comprise administering a compound having a structure as described herein and a pharmaceutically–acceptable carrier.

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METHOD OF TREATING HAIR LOSS USING KETOAMIDES

FIELD OF THE INVENTION

The present invention relates to methods for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth.

CROSS REFERENCE

This application claims priority under Title 35, United States Code § 119(e) from Provisional Application Serial No. 60/102,458, filed September 30, 1998.

BACKGROUND OF THE INVENTION

Hair loss is a common problem which occurs, for example, through natural processes or is often chemically promoted through the use of certain therapeutic drugs designed to alleviate conditions such as cancer. Often such hair loss is accompanied by lack of hair regrowth which causes partial or full baldness. Such baldness is cosmetically unappealing, and is particularly distressing to the person experiencing the hair loss.

As is well-known in the art, hair growth occurs by a cycle of activity which involves alternating periods of growth and rest. This cycle is often divided into three main stages which are known as anagen, catagen, and telogen. Anagen is the growth phase of the cycle and may be characterized by penetration of the hair follicle deep into the dermis with rapid proliferation of cells which are differentiating to form hair. The next phase is catagen, which is a transitional stage marked by the cessation of cell division, and during which the hair follicle regresses through the dermis and hair growth is ceased. The next phase, telogen, is often characterized as the resting stage during which the regressed follicle contains a germ with tightly packed dermal papilla cells. At telogen, the initiation of a new anagen phase is caused by rapid cell proliferation

in the germ, expansion of the dermal papilla, and elaboration of basement membrane components. This cycle is repeated throughout hair growth. Wherein hair growth ceases, most of the hair follicles reside in telogen and anagen is not engaged, thus causing the onset of full or partial baldness.

There have been many attempts in the literature to invoke the regrowth of hair by, for example, the promotion or prolongation of anagen. Currently, there are two drugs approved by the United States Food and Drug Administration for the treatment of male pattern baldness: topical minoxidil (marketed as Rogaine® by Pharmacia & Upjohn), and oral finasteride (marketed as Propecia® by Merck & Co., Inc.).

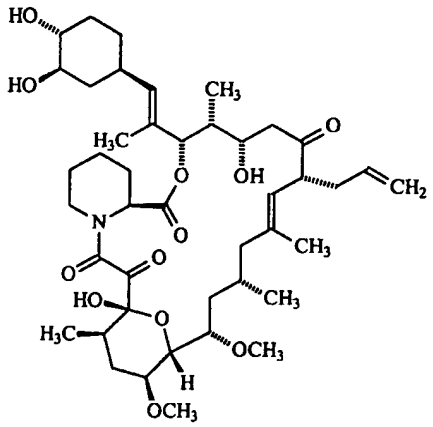
There are conflicting reports, however, regarding the ability of minoxidil to grow hair. In fact, early clinical studies investigating decreased blood pressure *via* the use of minoxidil did not even mention hypertrichosis (hair growth) as a side effect. See Dormois et al., "Minoxidil in Severe Hypertension: Value When Conventional Drugs Have Failed", American Heart Journal, Vol. 90, pp. 360 - 368 (1975). Indeed, the manufacturers of minoxidil have reported only limited hair growth in a portion of patients using minoxidil. See, e.g., Physician's Desk Reference®, 49th Ed. (1995), p. 2580. Furthermore, serious side effects of minoxidil are possible, including vasodilation (which leads to retention of fluid around the heart and increased heart rate), difficulty in breathing, and weight gain. Physician's Desk Reference®, 49th Ed. (1995), p. 2581.

Furthermore, while early indicators show that Propecia® may be more effective than Rogaine®, patients using Propecia® are experiencing limited hair growth. See The New England Journal of Medicine, Vol. 338, No. 9, February 26, 1998. Furthermore, potential side effects of Propecia® are serious. Propecia® may cause impotence, decreased sexual drive, decreased volume of ejaculate, breast tenderness and enlargement, and hypersensitivity reactions, including lip swelling and skin rash. Furthermore, Propecia® is not indicated for women and children. In fact, women who are pregnant or potentially pregnant should not even handle crushed or broken tablets containing the drug. See Physician's Desk Reference®, 52th Ed. (1998), p. 1737 and The New England Journal of Medicine, Vol. 338, No. 9, February 26, 1998.

Interestingly, the immunosuppressive agents cyclosporin A and FK506 are known to invoke a prominent hypertrichotic side effect. See Iwabuchi et al., "Effects of Immunosuppressive Peptidyl-Prolyl cis-trans Isomerase (PPIase) Inhibitors, Cyclosporin A, FK506, Ascomycin, and Rapamycin, on Hair Growth Initiation in Mouse: Immunosuppression is not Required for New Hair Growth", Journal of Dermatological Science, Vol. 9, pp. 64 - 69 (1995); Yamamoto et al., "Hair Growth-Stimulating Effects of Cyclosporin A and FK506, Potent Immunosuppressants", Journal of Dermatological Science, Vol. 7 (suppl.), pp. S47 - S54 (1994);

Yamamoto et al., "Stimulation of Hair Growth by Topical Application of FK506, a Potent Immunosuppressive Agent", Journal of Investigational Dermatology, Vol. 102, pp. 160 - 164 (1994); Jiang et al., "Induction of Anagen in Telogen Mouse Skin by Topical Application of FK506, a Potent Immunosuppressant", Journal of Investigational Dermatology, Vol. 104, pp. 523 - 525 (1995); McElwee et al., "Topical FK506: A Potent Immunotherapy for Alopecia Areata? Studies Using the Dundee Experimental Bald Rat Model", British Journal of Dermatology, Vol. 137, pp. 491 - 497 (1997); Maurer et al., "Hair Growth Modulation by Topical Immunophilin Ligands", American Journal of Pathology, Vol. 150, No. 4, pp. 1433 - 1441 (1997); and Paus et al., "Hair Growth Control by Immunosuppression", Arch. Dermatol. Res., Vol. 288, pp. 408 - 410 (1996). However, use of these compounds as hair growth actives may not be desirable due to their striking potency as immunosuppressive agents.

FK506 is a complex, macrocyclic molecule having the following structure:



Stocks et al., "The Contribution to Binding of the Pyranoside Substituents in the Excised Binding Domain of FK-506", Bioorganic & Medicinal Chemistry Letters, Vol.. 4, No. 12, pp. 1457 - 1460 (1994). Analogs closely resembling this complex macrocycle have been disclosed as having hair growth properties in the form of, for example, alopecia areata and / or male pattern baldness. See, e.g., Kawai et al., U.S. Patent No. 5,541,193, assigned to Abbott Laboratories, issued July 30,1996; Asakura et al., U.S. Patent No. 5,496,564, assigned to Fujisawa Pharmaceutical Co., issued March 5, 1996; Baumann et al., U.S. Patent No. 5,352,671 assigned to Sandoz Ltd., issued October 4, 1994; and Rupprecht et al., U.S. Patent No. 5,550,233, assigned to Merck & Co., Inc., issued August 27, 1996.

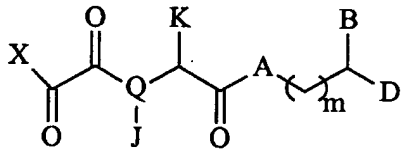
However, excitement related to the hypertrichotic activities of cyclosporin A and FK506 is somewhat quelled by the lack of reports of hypertrichosis by various smaller, non-macrocyclic immunosuppressive and non-immunosuppressive compounds which are less complex in structure than FK506. See Steiner et al., WO 96/40140, assigned to Guilford Pharmaceuticals, Inc.,

published December 19, 1996; Hamilton et al., WO 96/40633, assigned to Guilford Pharmaceuticals, Inc., published December 19, 1996; Steiner et al., U.S. Patent No. 5,696,135, assigned to GPI NIL Holdings, Inc., issued December 9, 1997; Hamilton et al., U.S. Patent No. 5,614,547, assigned to Guilford Pharmaceuticals, Inc., issued March 25, 1997; Steiner et al., WO 97/16190, assigned to Guilford Pharmaceuticals, Inc., published May 9, 1997; Zelle et al., WO 96/36630, assigned to Vertex Pharmaceuticals, Inc., published November 21, 1996; Armistead et al., WO 97/36869, assigned to Vertex Pharmaceuticals, Inc., published October 9, 1997; Zelle et al., WO 96/15101, assigned to Vertex Pharmaceuticals, Inc., published May 23, 1996; Armistead et al., WO 92/19593, assigned to Vertex Pharmaceuticals, Inc., published November 12, 1992; Armistead et al., WO 94/07858, assigned to Vertex Pharmaceuticals, Inc., published April 14, 1994; Zelle et al., WO 95/26337, assigned to Vertex Pharmaceuticals, Inc., published October 5, 1995; Duffy et al., WO 92/21313, assigned to Vertex Pharmaceuticals, Inc., published December 10, 1992; Armistead et al., U.S. Patent No. 5,192,773, assigned to Vertex Pharmaceuticals, Inc., issued March 9, 1993; Armistead et al., U.S. Patent No. 5,330,993, assigned to Vertex Pharmaceuticals, Inc., issued July 19, 1994; Armistead et al., U.S. Patent No. 5,622,970, assigned to Vertex Pharmaceuticals, Inc., issued April 22, 1997; Armistead et al., U.S. Patent No. 5,654,332, assigned to Vertex Pharmaceuticals, Inc., issued August 5, 1997; Armistead et al., U.S. Patent No. 5,620,971, assigned to Vertex Pharmaceuticals, Inc., issued April 15, 1997; Zelle et al., U.S. Patent No. 5,543,423, assigned to Vertex Pharmaceuticals, Inc., issued August 6, 1996; Armistead et al., U.S. Patent No. 5,516,797, assigned to Vertex Pharmaceuticals, Inc., issued May 14, 1996; Armistead et al., U.S. Patent No. 5,665,774, assigned to Vertex Pharmaceuticals, Inc., issued September 9, 1997; Andres et al., "Conformationally Defined Analogs of Prolylamides. *trans*-Prolyl Peptidomimetics", Journal of Organic Chemistry, Vol. 58, pp. 6609 - 6613 (1993); and Armistead et al., "Design, Synthesis and Structure of Non-macrocyclic Inhibitors of FKBP12, the Major Binding Protein for the Immunosuppressant FK506", Acta Crystallographica, D51, pp. 522 - 528 (1995).

Surprisingly, the present inventors have discovered a class of compounds which arrest and / or reverse hair loss or promote hair growth but do not share the complex, macrocyclic structure of FK506. The present inventors have further discovered compounds among this class which invoke hair growth yet are surprisingly non-immunosuppressive or are nominally immunosuppressive. The minimized and / or absent immunosuppressive activity of these hypertrichotic compounds are distinct advantages as compared to the immunosuppressive compounds cyclosporin A and FK506. The present inventors therefore provide methods of treating hair loss by administering compositions comprising the compounds described herein.

SUMMARY OF THE INVENTION

The present invention relates to methods for treating hair loss comprising administering compounds which have been found by the present inventors to be particularly useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. The compounds utilized in the present method have the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein X, J, K, A, B, D, Q, and m are defined herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of using compounds and compositions which are particularly useful for treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth.

In addition to discovering that the present compounds are useful for treating hair loss, the present inventors have also surprisingly discovered that immunosuppression is not required for hair growth stimulation. The present inventors have further discovered compounds that are useful for treating hair loss but are surprisingly non-immunosuppressive. Preferred compounds useful in the method of the present invention are therefore, as defined herein, non-immunosuppressive.

Publications and patents are referred to throughout this disclosure. All references cited herein are hereby incorporated by reference.

All percentages, ratios, and proportions used herein are by weight unless otherwise specified.

Definition and Usage of Terms

The following is a list of definitions for terms used herein:

As used herein "salt" is a cationic salt formed at any acidic (*e.g.*, carboxyl) group, or an anionic salt formed at any basic (*e.g.*, amino) group. Many such salts are known in the art. Preferred cationic salts include the alkali metal salts (such as, for example, sodium and potassium), alkaline earth metal salts (such as, for example, magnesium and calcium), and

organic salts. Preferred anionic salts include the halides (such as, for example, chloride salts). Such acceptable salts must, when administered, be appropriate for mammalian use.

As used herein, "alkenyl" is an unsaturated hydrocarbon chain radical. Alkenyls have at least one olefinic double bond. Unless otherwise specified, alkenyls have from 2 to about 15 carbon atoms (C_2 - C_{15}); preferably from 2 to about 10 carbon atoms (C_2 - C_{10}); more preferably from 2 to about 8 carbon atoms (C_2 - C_8), and most preferably from about 2 to about 6 carbon atoms (C_2 - C_6). Non-limiting examples of alkenyls include vinyl, allyl, and butenyl.

As used herein, "alkoxy" is an oxygen radical having an alkyl, alkenyl, or alkynyl, preferably an alkyl or alkenyl, and most preferably an alkyl substituent. Examples of alkoxy radicals include -O-alkyl and -O-alkenyl..

As used herein, "alkyl" is a saturated hydrocarbon chain radical. Unless otherwise specified, alkyls have from 1 to about 15 carbon atoms (C_1 - C_{15}); preferably from 1 to about 10 carbon atoms (C_1 - C_{10}); more preferably from 1 to about 6 carbon atoms (C_1 - C_6); and most preferably from 1 to about 4 carbon atoms (C_1 - C_4). Preferred alkyls include, for example, methyl, ethyl, propyl, *iso*-propyl, and butyl.

As used herein, "alkylene" refers to an alkyl, alkenyl, or alkynyl which is a diradical. For example, "methylene" is -CH_2-.

As used herein, "alkynyl" is an unsaturated hydrocarbon chain radical. Alkynyls have at least one triple bond. Unless otherwise specified, alkynyls have from 2 to about 15 carbon atoms (C_2 - C_{15}); preferably from 2 to about 10 carbon atoms (C_2 - C_{10}); more preferably from 2 to about 8 carbon atoms (C_2 - C_8), and most preferably from about 2 to about 6 carbon atoms (C_2 - C_6).

As used herein, "biohydrolyzable amides" are amides of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable esters" are esters of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "biohydrolyzable imides" are imides of the compounds used in the present invention which do not interfere with the activity of the compound, or that are readily converted *in vivo* by a mammalian subject to yield an active compound.

As used herein, "carbocyclic ring", "carbocycle", or the like is a hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocyclic rings contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycyclic rings contain from about

7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms.

As used herein, "cycloalkyl" is a saturated carbocyclic or heterocyclic ring radical. Preferred cycloalkyl groups include, for example, cyclobutyl, cyclopentyl, and cyclohexyl.

As used herein, "heteroalkenyl" is an alkenyl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen.

As used herein, "heteroalkyl" is an alkyl radical comprised of carbon atoms and one or more heteroatoms wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen.

As used herein, "heterocyclic ring", "heterocycle", or the like is a ring radical comprised of carbon atoms and one or more heteroatoms in the ring wherein the heteroatoms are selected from the group consisting of oxygen, sulfur, nitrogen, and phosphorous, more preferably, oxygen, sulfur, and nitrogen. Heterocycles are monocyclic or are fused, bridged, or spiro polycyclic rings. Unless otherwise specified, monocycles contain from 3 to about 9 atoms, preferably from about 4 to about 7 atoms, and most preferably 5 or 6 atoms. Polycycles contain from about 7 to about 17 atoms, preferably from about 7 to about 14 atoms, and most preferably 9 or 10 atoms. Heterocyclic rings (heterocycles) may be substituted or unsubstituted.

As used herein, a "lower" moiety (*e.g.*, "lower" alkyl) is moiety having 1 to about 6, preferably 1 to about 4, carbon atoms.

As used herein, "pharmaceutically acceptable" means suitable for use in a human or other mammal.

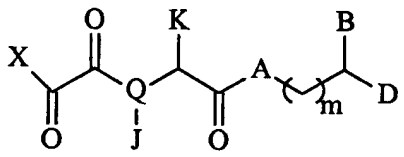
As used herein, "safe and effective amount of a compound" (or composition, or the like) means an amount that is effective to exhibit biological activity, preferably wherein the biological activity is arresting and / or reversing hair loss or promoting hair growth, at the site(s) of activity in a mammalian subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit / risk ratio when used in the manner of this invention.

As used herein, wherein any variable, moiety, group, or the like occurs more than one time in any variable or structure, its definition at each occurrence is independent of its definition at every other occurrence.

Methods of the Present Invention

The present invention relates to methods of treating hair loss comprising administering a composition comprising:

(a) a compound having the structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein:

(i) Q is a first heteroatom, wherein the first heteroatom is nitrogen;

(ii) A is selected from CH_2, O, S, and NR_1;

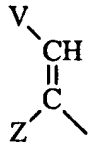
(iii) R_1 is selected from the group consisting of hydrogen and alkyl;

(iv) J is selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_6 alkenyl, benzyl, Ar substituted C_1 - C_6 alkyl, Ar substituted C_3 - C_6 alkenyl, Ar substituted C_3 - C_6 alkynyl; K is selected from C_1 - C_6 alkyl, Ar substituted C_1 - C_6 alkyl, Ar substituted C_2 - C_6 alkenyl, Ar substituted C_2 - C_6 alkynyl, and cyclohexylmethyl; or J and K may be bonded together to form a 5-, 6-, or 7-membered heterocyclic ring wherein the ring may optionally contain an additional heteroatom selected from O, S, S(O), $S(O)_2$, NH, and NE, wherein when B and D are bonded together to form a substituted or unsubstituted tetrahydronapthalene moiety, J and K may be optionally bonded together to form a 5- or 6-membered carbocyclic ring which is fused to a phenyl ring;

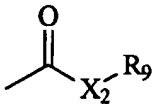
(v) X is selected from hydrogen, C_1 - C_9 alkyl, C_2 - C_9 alkenyl, C_5 - C_7 cycloalkyl, C_5 - C_7 cycloalkyl, C_5 - C_7 cycloalkenyl, C_5 - C_7 cycloalkenyl, Ar, $-OR_2$, [C_1 - C_4 alkyl]-Y, [C_2 - C_4 alkenyl]-Y, Y, and $-NR_3R_4$;

(vi) R_2, R_3, R_4, B, D, and E are each, independently, selected from nil, hydrogen, Ar, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_5 - C_7 cycloalkyl substituted C_1 - C_6 alkyl, C_5 - C_7 cycloalkyl substituted C_3 - C_6 alkenyl, C_5 - C_7 cycloalkyl substituted C_3 - C_6 alkynyl, C_5 - C_7 cycloalkenyl substituted C_1 - C_6 alkyl, C_5 - C_7 cycloalkenyl substituted C_3 - C_6 alkenyl, C_5 - C_7 cycloalkenyl substituted C_3 - C_6 alkynyl, Ar substituted C_1 - C_6 alkyl, Ar substituted C_3 - C_6 alkenyl, and Ar substituted C_3 - C_6 alkynyl; wherein one or more CH_2 moieties of the alkyls, alkenyls, and alkynyls may be optionally replaced by a heteroatom selected from O, S, S(O), $S(O)_2$, and NR, wherein

R is selected from hydrogen, C_1 - C_4 alkyl, C_3 - C_4 alkenyl, C_3 - C_4 alkynyl, and C_1 - C_4 bridging alkyl wherein a bridge is formed between the N of NR and a carbon atom of the heteroatom-containing alkyl, alkenyl, or alkynyl to form a bridging ring, and wherein the bridging ring is optionally fused to Ar; wherein B and D may also be bonded together to form a 5-, 6-, or 7-membered carbocyclic ring which is optionally fused with an aryl; wherein B and D may also be each, independently:



wherein Z is selected from hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, and C_2 - C_6 alkynyl, and V is selected from Ar and substituted 5-, 6-, or 7-membered carbocyclic ring having substituents which are independently selected from oxo, hydrogen, hydroxyl, O-(C_1 - C_4 alkyl), and O-(C_2 - C_4 alkenyl); wherein B may also be T, wherein T has the structure:



wherein X_2 is selected from O and NR_{10}, wherein R_{10} is selected from hydrogen, C_1 - C_6 alkyl, and C_1 - C_6 alkenyl; and R_9 is selected from phenyl, benzyl, C_1 - C_5 alkyl, C_1 - C_5 alkenyl, C_1 - C_5 alkyl substituted with phenyl, and C_1 - C_5 alkenyl substituted with phenyl; wherein when B is T, then D is R_8, wherein R_8 is selected from C_1 - C_8 alkyl optionally substituted with C_3 - C_8 cycloalkyl, and Ar; and wherein R_3 and R_4 may also be bonded together to form a 5-, 6-, or 7-membered heterocyclic aliphatic or aromatic ring;

(vii) Ar and Y are each, independently, selected from phenyl, benzyl, 1-napthyl, 2-napthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, 1,2,3,4,-

tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-napthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, and quinuclidinyl; wherein Ar bears one or more substituents independently selected from hydrogen, halogen, hydroxyl, nitro, $-SO_3H$, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, O-[C_1 - C_6 alkyl], O-[C_2 - C_4 alkenyl], O-benzyl, O-phenyl, 1,2,-methylenedioxy, $-NR_5R_6$, carboxyl, N-[C_1 - C_5 alkyl] carboxamide, N-[C_3 - C_5 alkenyl] carboxamide, N,N-di-[C_1 - C_5 alkyl] carboxamide, N,N-di-[C_3 - C_5 alkenyl] carboxamide, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, morpholinyl, piperidinyl, O-M, CH_2-$(CH_2)_q$-M, O-$(CH_2)_q$-M, $(CH_2)_q$-O-M, and CH=CH-M; wherein R_5 and R_6 are each, independently, selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, and benzyl, or R_5 and R_6 may be bonded together to form a 5- or 6-membered heterocyclic ring; M is selected from 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl; and q is an integer from 0 to 2; and wherein Y bears one or more substituents independently selected from hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, O-[C_1 - C_4 alkyl], O-[C_2 - C_4 alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl; and

(viii) m is an integer from 0 to 3; and

(b) a pharmaceutically-acceptable carrier.

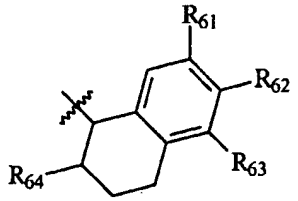
The X Moiety

The compounds used in the present method comprise a moiety attached to the diketoamide moiety which is referred to herein as the X Moiety, or X. X is selected from hydrogen, C_1 - C_9 alkyl, C_2 - C_9 alkenyl, C_5 - C_7 cycloalkyl, C_5 - C_7 cycloalkyl, C_5 - C_7 cycloalkenyl, C_5 - C_7 cycloalkenyl, Ar, $-OR_2$, [C_1 - C_4 alkyl]-Y, [C_2 - C_4 alkenyl]-Y, Y, and $-NR_3R_4$. As stated herein above, all moieties may be unsubstituted or substituted, but wherein X is substituted cycloalkyl or cycloalkenyl, the preferred substituents on such X moiety cycles are

C_1 - C_4 alkyl or hydroxy or C_2 - C_4 alkenyl. Ar, R_2, Y, R_3, and R_4 are described elsewhere herein. When X is Ar, the preferred Ar moieties are selected from phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, imidazolyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, and 1,2,3,4-tetrahydroquinolinyl. As stated herein all moieties may be unsubstituted or substituted, but wherein X is substituted Ar then preferred substituents include hydroxyl, nitro, trifluoromethyl, C_1 - C_6 alkyl, O-[C_1 - C_6 alkyl], halogen, -SO_3H, and -NR_5R_6, wherein R_5 and R_6 are described herein above. The more preferred X moieties are selected from 3,4,5-trimethoxyphenyl, *iso*-propyl, phenyl, *tert*-butyl, thiophenyl-2-yl, 3-benzyloxyphenyl, 3-allyloxyphenyl, 2-furyl, and 3-isopropoxyphenyl. The most preferred X moiety is 3,4,5-trimethoxyphenyl.

The J and K Moieties

The J and K moieties may be independent of each other having the above described structures or, as stated, may be bonded together to form a 5-, 6-, or 7-membered heterocyclic ring optionally containing an additional heteroatom selected from O, S, S(O), $S(O)_2$, NH, and NE. When B and D are bonded together to form a substituted or unsubstituted tetrahydronapthalene moiety, J and K may be optionally bonded together to form a 5- or 6-membered carbocyclic ring which is fused to a phenyl ring. As used herein, substituted or unsubstituted tetrahydronapthalene moiety is:



wherein R_{61}, R_{62}, and R_{63} are each, independently, selected from hydrogen, halogen, alkyl, O-alkyl, $(CH_2)_b$-aryl, and $R_{50}(CH_2)_b$-aryl, wherein R_{50} is selected from O, S, and NR_{51}; wherein R_{51} is selected from alkyl and hydrogen; b is an integer from 0 to 4; and R_{64} is selected from hydrogen and $(CH2)_c$-R_{52}, wherein R_{52} is selected from aryl and $NR_{53}R_{54}$, wherein R_{53} and R_{54} are each, independently, selected from hydrogen, alkyl, and (CH_2)-aryl, or wherein R_{53} and R_{54} are bonded together to form a 5- or 6-membered heterocyclic ring; and c is an integer from 1 to 3.

Wherein J and K form the heterocyclic ring, the ring is preferably 5- or 6-membered. Wherein J and K form the heterocyclic ring, the ring preferably does not contain any additional heteroatoms other than the Q nitrogen required at the 1-position of the cycle as shown herein.

The A Moiety

A is selected from CH_2, O, S, and NR_1, wherein R_1 is described herein. Preferably, A is selected from O and NR_1. Most preferably A is NR_1. In such cases, R_1 is most preferably hydrogen.

The B and D Moieties

B and D are side chains which are selected from a variety of moieties described herein above.

Preferred B moieties are selected from hydrogen, alkyl, alkenyl, 3-(2-pyridyl)propyl, 3-phenylpropyl, 2-phenoxyphenyl, 3-phenoxyphenyl, phenyl, benzyl, 2-(3-pyridyl)ethyl, E-3-[trans-(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl, E-3-[trans-(4-hydroxycyclohexyl)]-2-methyl-eth-2-enyl, 3-(3-pyridyl)propyl, 2-phenylethyl, 2-(4-methoxyphenyl)ethyl, 3-(N-benzimidazolyl)propyl, 3-(4-methoxyphenyl)propyl, 3-[N-(7-azaindolyl)propyl, 3-(N-purinyl)propyl, 3-(3-pyridyl)-N-oxide, 3-(4-hydroxymethylphenyl)propyl, 3-(2-thienyl)propyl, 3-(4-carboxyphenyl)propyl, 4-phenylbutyl, 2-hydroxymethylphenyl, 2-allyloxyphenyl, 3-(3-hydroxymethylphenyl)propyl, 3-(3-carboxyphenyl)propyl, 3-hydroxymethylphenyl, 2-hydroxyphenyl, 3-pyridyl, 5-phenylpentyl, 4-(4-methoxyphenyl)butyl, 4-cyclohexylbutyl, 3-cyclohexylpropyl, 3-cyclopentylpropyl, 3-phenoxybenzyl, and 3-(3-indolyl)propyl.

Preferred D moieties are selected from nil, hydrogen, 3-phenylpropyl, 2-phenoxyphenyl, 3-(3-indolyl)-propyl, 2-phenylethyl, 4-phenylbutyl, 3,5-bis(benzyloxy)phenyl, alkyl, alkenyl, phenyl, and 3-(4-methoxyphenyl)propyl.

The Integer m

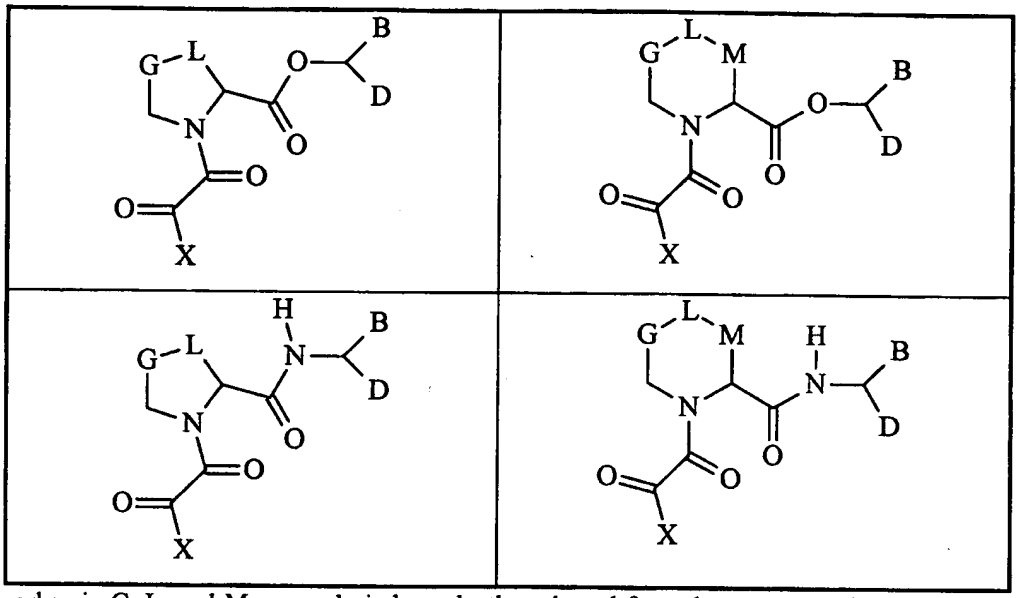
The integer m is from 0 to 3, preferably from 0 to 1.

Preferred Ar Moieties

The Ar moiety is defined herein above. Preferred Ar moieties are selected from phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, imidazolyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 2-furyl, and 1,2,3,4,-tetrahydroquinolinyl, wherein Ar has one or more substituents each independently selected from the group consisting of hydrogen, hydroxyl, nitro, trifluoromethyl, C_1 - C_6 alkyl, O-[C_1 - C_6 alkyl], halogen, -SO_3H, and -NR_5R_6, wherein R_5 and R_6 are described herein above.

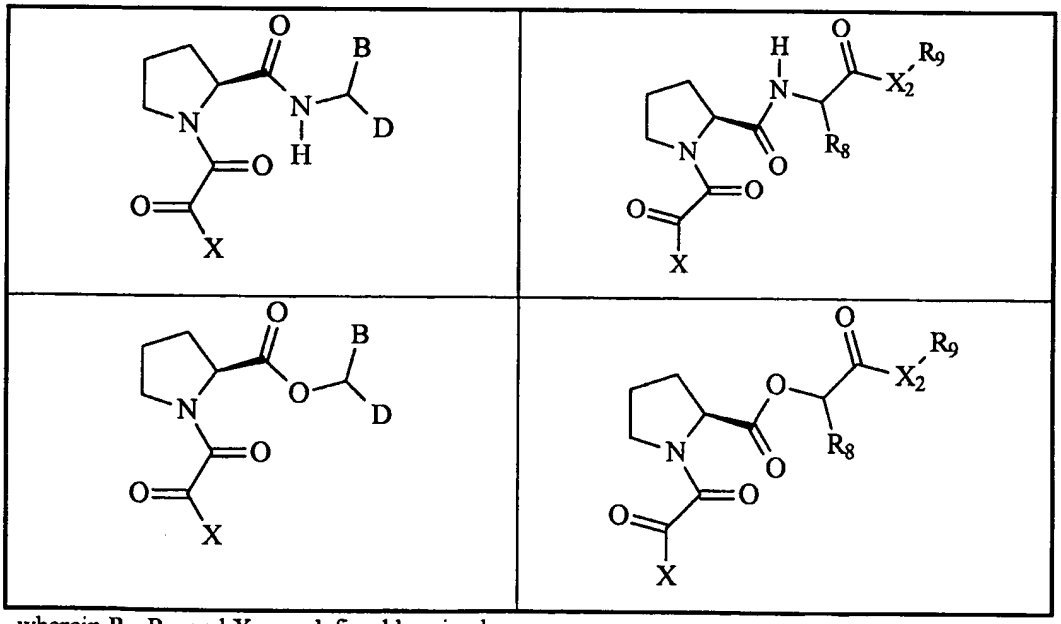
Preferred compounds useful in the methods of the present invention are shown in the tables below:

Table 1



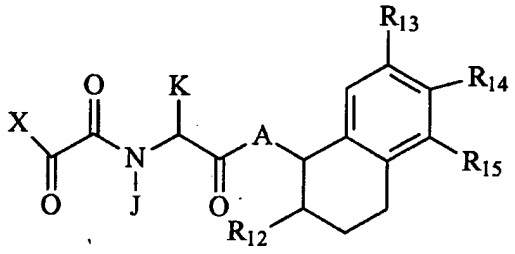
wherein G, L, and M are each, independently, selected from the group consisting of CH_2, S, O, NH, and NE, wherein E is defined herein above.

Table 2



wherein R_8, R_9, and X_2 are defined herein above.

Other preferred compounds useful in the present method include those wherein B and D are bonded together to form a 5-, 6-, or 7-membered carbocyclic ring which is fused with an aromatic ring, such as:



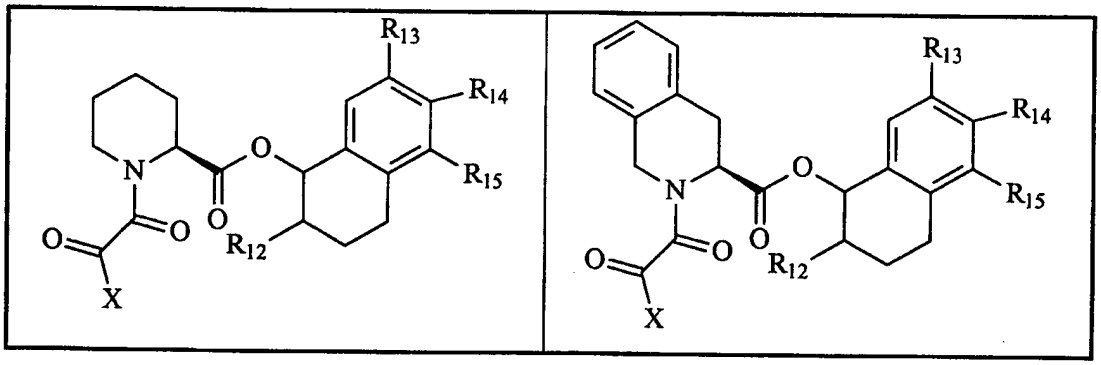
wherein:

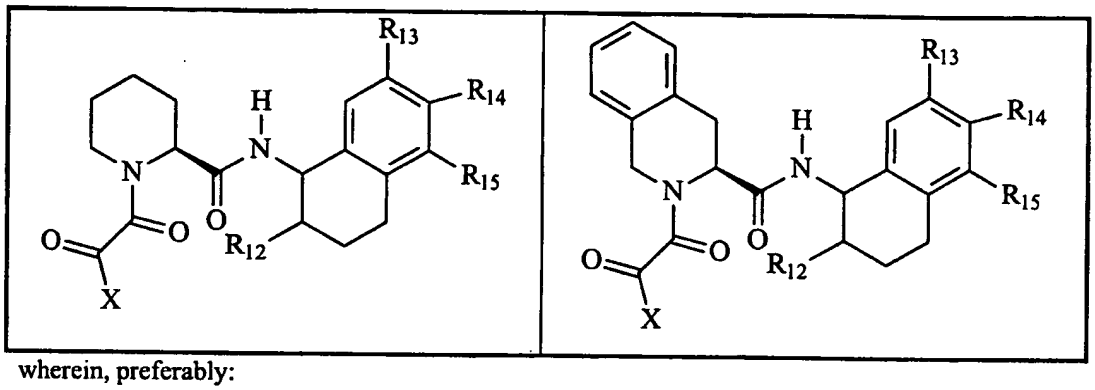
(a) R_{12} is selected from hydrogen and $-(CH_2)_t-R_{16}$, wherein t is an integer from 1 to 3 and R_{16} is selected from the group consisting of Ar and $NR_{17}R_{18}$, wherein R_{17} and R_{18} are each, independently, selected from hydrogen, C_1 - C_5 alkyl, and $-(CH_2)$-Ar, or R_{17} and R_{18} may be bonded together to form a 5- or 6-membered heterocyclic ring; and

(b) R_{13}, R_{14}, and R_{15} are each, independently, selected from hydrogen, halogen, C_1 - C_6 alkyl, O-(C_1 - C_6 alkyl), $-(CH_2)_e$-Ar, and $-G(CH_2)_e$-Ar, wherein e is an integer from 0 to 4; and G is selected from the group consisting of O, S, and NR_{19}, wherein R_{19} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl; and

(c) A is selected from -O- and -NH-.

Table 3





wherein, preferably:

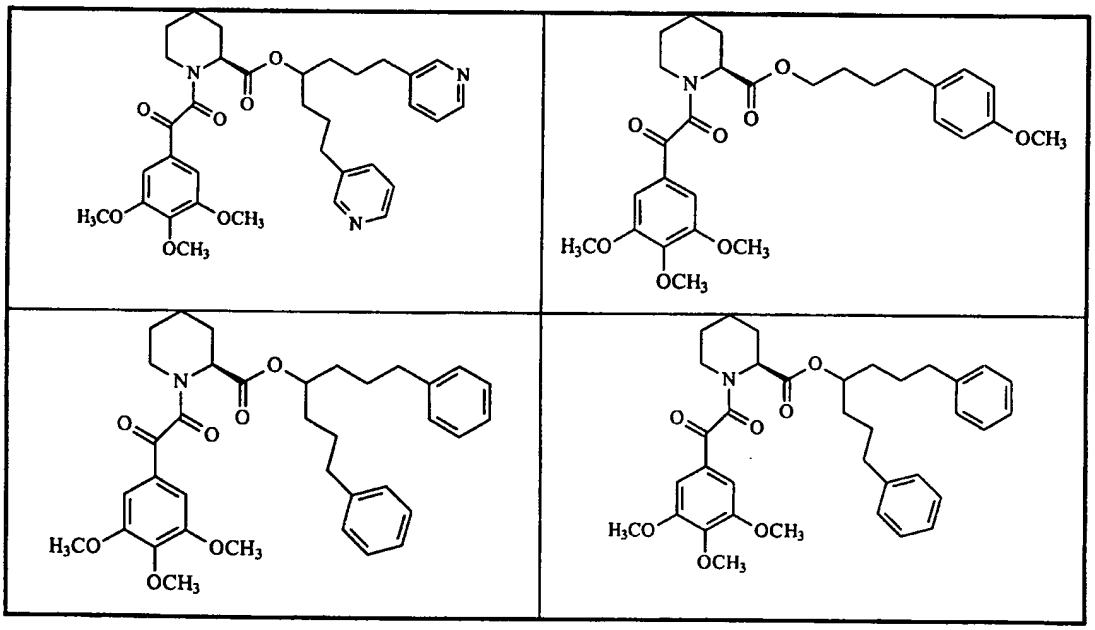
(a) R_{13} are R_{15} are each, independently, selected from -OCH_2-4-pyridine, -O-propyl, and hydrogen;

(b) R_{14} is selected from -OCH_2-4-pyridine, methyl, and hydrogen;

(c) R_{12} is selected from -CH_2-3-pyridine and hydrogen; and

(d) X is 3,4,5-trimethoxyphenyl.

Table 4



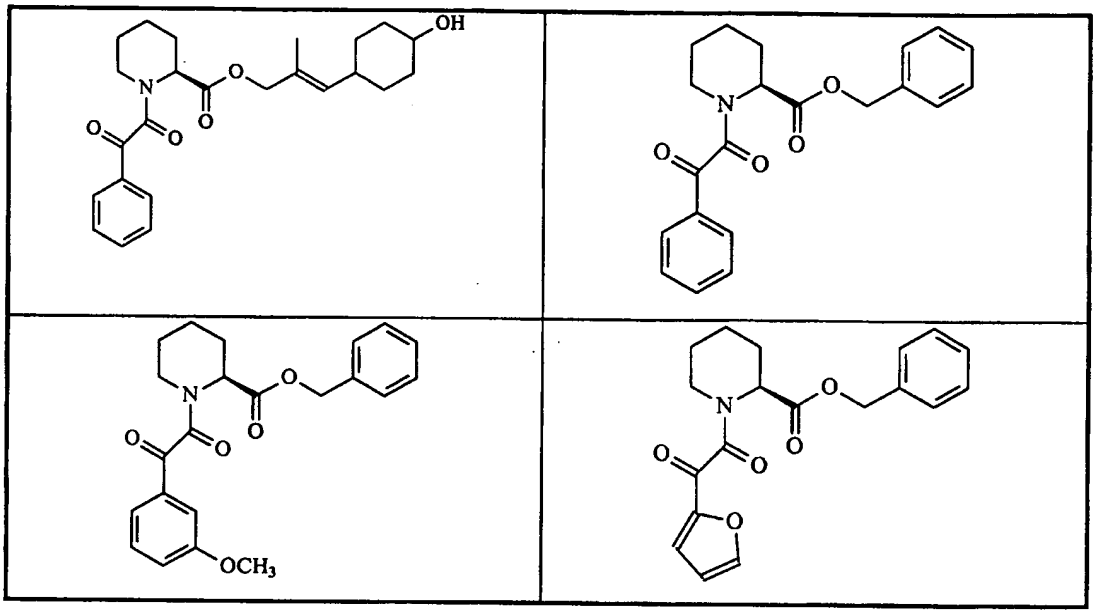
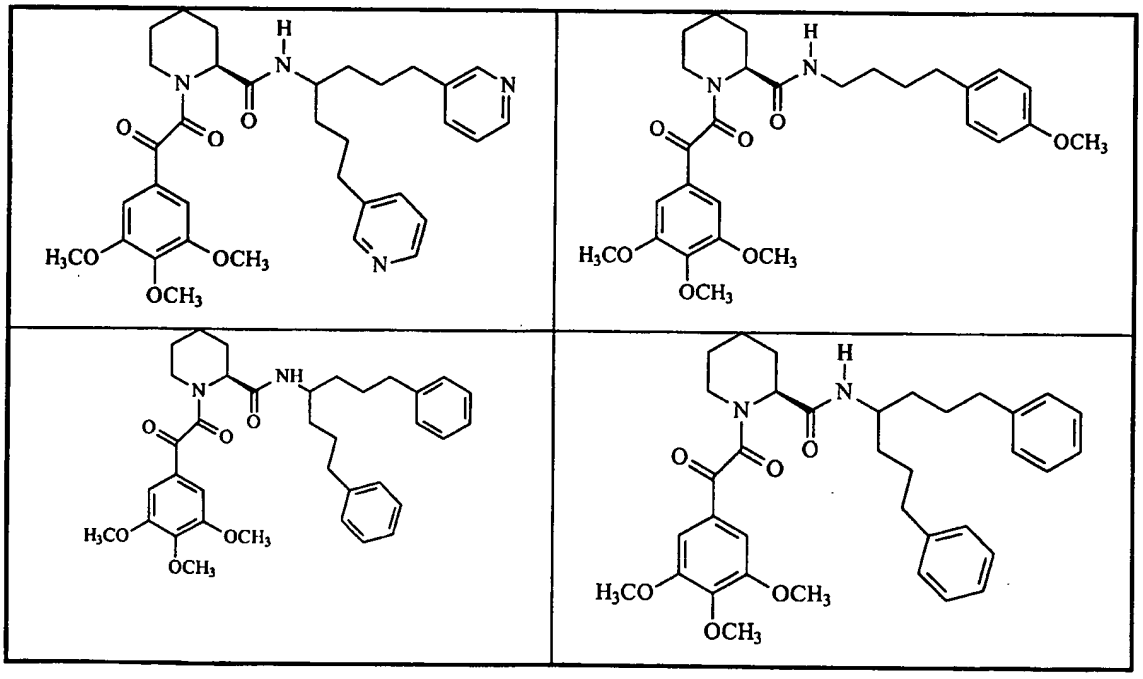
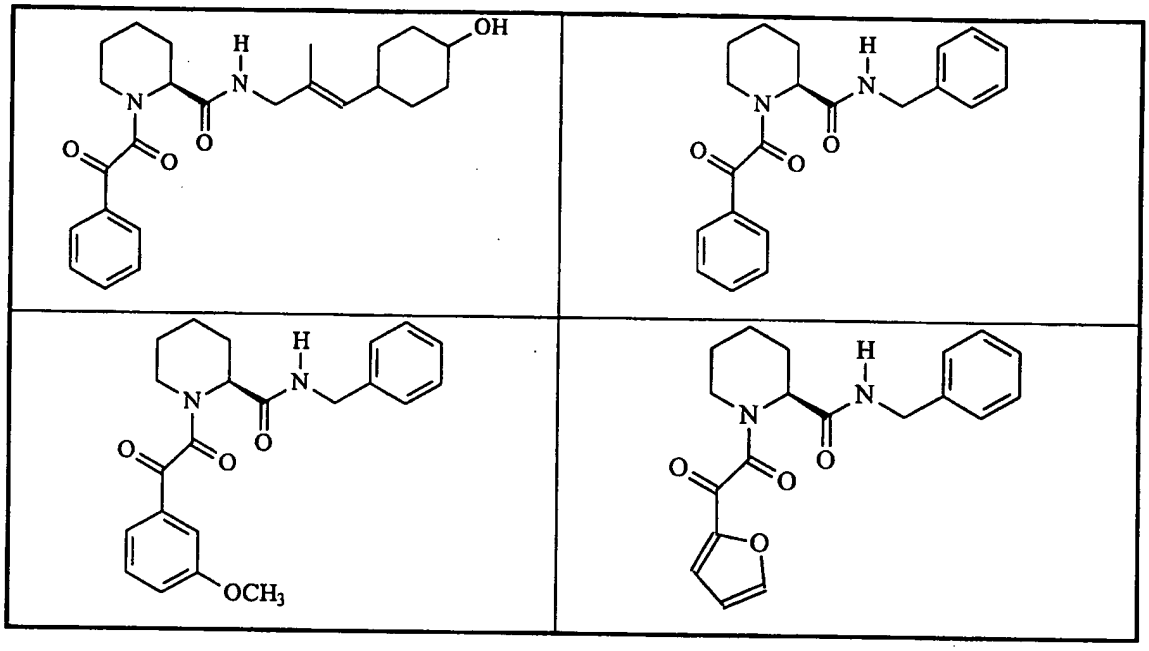


Table 5





Other preferred compounds useful in the method of the present invention include:

(a) 3-phenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(b) 3-phenyl-1-prop-2-(E)-enyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(c) 3-(3,4,5-trimethoxyphenyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(d) 3-(3,4,5-trimethoxyphenyl)-1-prop-2-(E)-enyl (2S)-1-(3,3-dimethyl-1,2-dioxopenyl)-2-pyrrolidinecarboxylate;

(e) 3-(4,5-dichlorophenyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(f) 3-(4,5-dichlorophenyl)-1-prop-2-(E)-enyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(g) 3-(4,5-methylenedioxyphenyl)-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(h) 3-(4,5-methylenedioxyphenyl)-1-prop-2-(E)-enyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(i) 3-cyclohexyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(j) 3-cyclohexyl-1-prop-2-(E)-enyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(k) (1R)-1,3-diphenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)- 2-pyrrolidinecarboxylate;

(l) (1R)-1,3-diphenyl-1-prop-2-(E)-enyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)- 2-pyrrolidinecarboxylate;

(m) (1R)-1-cyclohexyl-3-phenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)- 2-pyrrolidinecarboxylate;

(n) (1R)-1-cyclohexyl-3-phenyl-1-prop-2-(E)-enyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)- 2-pyrrolidinecarboxylate;

(o) (1R)-1-(4,5-dichlorophenyl-3-phenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)- 2-pyrrolidinecarboxylate;

(p) 3-phenyl-1-propyl (2S)-1-(1,2-dioxo-2-cyclohexyl)ethyl- 2-pyrrolidinecarboxylate;

(q) 3-phenyl-1-propyl (2S)-1-(1,2-dioxo-4-cyclohexyl)butyl- 2-pyrrolidinecarboxylate;

(r) 3-phenyl-1-propyl (2S)-1-(1,2-dioxo-2-[furanyl])ethyl- 2-pyrrolidinecarboxylate;

(s) 3-phenyl-1-propyl (2S)-1-(1,2-dioxo-2-[thienyl])ethyl- 2-pyrrolidinecarboxylate;

(t) 3-phenyl-1-propyl (2S)-1-(1,2-dioxo-2-[2-thiazolyl])ethyl- 2-pyrrolidinecarboxylate;

(u) 3-phenyl-1-propyl (2S)-1-(1,2-dioxo-2-phenyl)ethyl- 2-pyrrolidinecarboxylate;

(v) 1,7-diphenyl-4-heptyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(w) 3-phenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxo-4-hydroxybutyl)-2-pyrrolidinecarboxylate;

(x) 3-phenyl-1-propyl (2S)-1-(3,3-dimethyl-1,2-dioxopentyl)-2-pyrrolidinecarboxylate;

(y) 1-[1-3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylalanine ethyl ester;

(z) 1-[1-3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-leucine ethyl ester;

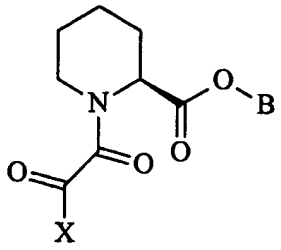
(aa) 1-[1-3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylglycine ethyl ester;

(bb) 1-[1-3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylalanine phenyl ester;

(cc) 1-[1-3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-phenylalanine benzyl ester; and

(dd) 1-[1-3,3-dimethyl-1,2-dioxopentyl)-L-proline]-L-isoleucine ethyl ester.

Table 6



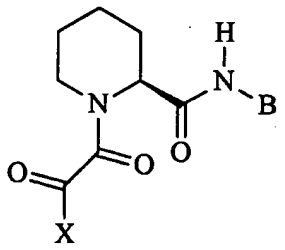
B	X
3-phenylpropyl	phenyl
4-(4-methoxyphenyl)butyl	phenyl
4-phenylbutyl	phenyl
4-cyclohexylbutyl	phenyl
benzyl	methoxy
4-cyclohexylbutyl	methoxy
3-cyclohexylpropyl	methoxy
3-cyclopentylpropyl	methoxy
4-cyclohexylbutyl	3,4,5-trimethoxyphenyl
3-phenoxybenzyl	3,4,5-trimethoxyphenyl
4-phenylbutyl	3,4,5-trimethoxyphenyl
3-(3-indolyl)propyl	3,4,5-trimethoxyphenyl
4-(4-methoxyphenyl)butyl	3,4,5-trimethoxyphenyl
benzyl	phenyl
allyl	phenyl
1-napthyl	phenyl
2-napthyl	phenyl
benzyl	2-methylpropyl
benzyl	2-methoxyphenyl
benzyl	3-methoxyphenyl
benzyl	4-methoxyphenyl
benzyl	3,5-dimethoxyphenyl
benzyl	2,6-dimethoxyphenyl
benzyl	3,4,5-trimethoxyphenyl
benzyl	4-fluorophenyl
benzyl	3-nitrophenyl

benzyl	4-nitrophenyl
benzyl	2-pyridyl
benzyl	2-pyridyl-N-oxide
benzyl	2-furyl
benzyl	3-indolyl
E-3-(4-hydroxyphenyl)-2-methyl-prop-2-enyl	phenyl
E-3-phenyl-2-methyl-prop-2-enyl	phenyl
E-3-[cis-(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl	phenyl
E-3-[trans-(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl	phenyl
benzyl	2-nitrobenzyl
benzyl	2-thiophenyl
hydrogen	methoxy
allyl	methoxy
benzyl	methoxy
2-cyclohexylethyl	methoxy
3-cyclohexylpropyl	methoxy
4-cyclohexylbutyl	methoxy
3-cyclopentylpropyl	methoxy
E-3-(4-methoxyphenyl)-2-methyl-prop-2-enyl	methoxy
E-3-(3,4-dimethoxyphenyl)-2-methyl-prop-2-enyl	methoxy
E-3-(4-hydroxyphenyl)-2-methyl-prop-2-enyl	methoxy
E-3-[cis-(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl	methoxy
benzyl	cyclohexyl
benzyl	3,4-difluorophenyl
benzyl	(E)-2-(4-methoxyphenyl)-ethenyl
benzyl	1-hydroxy-1-cyclohexyl
benzyl	2-napthyl
benzyl	1-napthyl

(S)-alpha-methylbenzyl	phenyl
benzyl	2-hydroxy-2-tetrahydropyranyl
(R)-alpha-methylbenzyl	phenyl
benzyl	3-trifluoromethylphenyl
benzyl	3-benzyloxyphenyl
benzyl	(E)-2-*tert*-butylethenyl
benzyl	2-trifluoromethylphenyl
4-cyclohexylbutyl	phenyl
4-cyclohexylbutyl	3,4,5-trimethoxyphenyl
4-phenylbenzyl	phenyl
4-phenylbenzyl	3,4,5-trimethoxyphenyl
benzyl	3-ethoxyphenyl
3-phenoxybenzyl	3,4,5-trimethoxyphenyl
3-phenoxybenyzl	phenyl
4-phenylbutyl	3,4,5-trimethoxyphenyl
4-phenylbutyl	phenyl
benzyl	3-(3-propenyloxy)phenyl
benzyl	3-(2-propoxy)phenyl
benzyl	1-methylpropyl
2-phenylethyl	phenyl
6-phenylhexyl	phenyl
5-phenylpentyl	3,4,5-trimethoxyphenyl
6-phenylhexyl	3,4,5-trimethoxyphenyl
6-cyclohexylhexyl	3,4,5-trimethoxyphenyl
4-phenoxybenzyl	3,4,5-trimethoxyphenyl
5-cyclohexylpentyl	3,4,5-trimethoxyphenyl
benzyl	3-(1-butoxy)phenyl
4-phenylbutyl	3-(2-propoxy)phenyl
4-(4-iodophenyl)butyl	3,4,5-trimethoxyphenyl
4-iodobenzyl	3,4,5-trimethoxyphenyl
2-(2-napthyl)ethyl	3,4,5-trimethoxyphenyl
2-(1-napthyl)ethyl	3,4,5-trimethoxyphenyl

4-phenylbutyl	4-iodophenyl
4-phenylbutyl	3-iodophenyl
3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(3-indolyl)propyl	3,4,5-trimethoxyphenyl
4-(4-methoxyphenyl)butyl	3,4,5-trimethoxyphenyl
4-phenylbut-2-enyl	3,4,5-trimethoxyphenyl
4-phenylbut-3-enyl	3,4,5-trimethoxyphenyl
4-(4-allocaminophenyl)propyl	3,4,5-trimethoxyphenyl
4-phenylpropyl	1-cyclohexenyl
4-(4-methoxyphenyl)but-3-enyl	3,4,5-trimethoxyphenyl
4-phenylpropyl	1-fluoro-1-cyclohexyl
4-phenylpropyl	3-butoxyphenyl
3-[3-(N-formylindolyl)]propyl	3,4,5-trimethoxyphenyl
4-(3-indolyl)butyl	3,4,5-trimethoxyphenyl
4-phenylbutyl	benzyl
4-phenylbutyl	3-biphenyl
4-phenylbutyl	4-*tert*-butylphenyl
4-phenylbutyl	cyclohexyl
4-phenylbutyl	cyclohexylmethyl
4-phenylbutyl	3,4-methylenedioxyphenyl
4-phenylbutyl	4-tetrahydropyranyl
4-phenylbutyl	3-cyclohexyl-4-methoxy-phenyl
4-phenylbutyl	4-(4-methoxybenzyloxy-methyl)-2-furyl
4-phenylbutyl	*tert*-butyl
4-phenylbutyl	ethyl
3-(N-benzimidazolyl)propyl	3,4,5-trimethoxyphenyl
3-(N-purinyl)propyl	3,4,5-trimethoxyphenyl
(S,S)-2-methyl-3-hydroxy-4-phenylpropyl	3,4,5-trimethoxyphenyl

Table 7



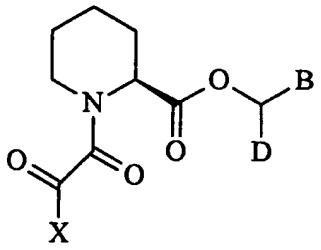
B	X
3-phenylpropyl	phenyl
4-(4-methoxyphenyl)butyl	phenyl
4-phenylbutyl	phenyl
4-cyclohexylbutyl	phenyl
benzyl	methoxy
4-cyclohexylbutyl	methoxy
3-cyclohexylpropyl	methoxy
3-cyclopentylpropyl	methoxy
4-cyclohexylbutyl	3,4,5-trimethoxyphenyl
3-phenoxybenzyl	3,4,5-trimethoxyphenyl
4-phenylbutyl	3,4,5-trimethoxyphenyl
3-(3-indolyl)propyl	3,4,5-trimethoxyphenyl
4-(4-methoxyphenyl)butyl	3,4,5-trimethoxyphenyl
benzyl	phenyl
allyl	phenyl
1-napthyl	phenyl
2-napthyl	phenyl
benzyl	2-methylpropyl
benzyl	2-methoxyphenyl
benzyl	3-methoxyphenyl
benzyl	4-methoxyphenyl
benzyl	3,5-dimethoxyphenyl
benzyl	2,6-dimethoxyphenyl
benzyl	3,4,5-trimethoxyphenyl
benzyl	4-fluorophenyl

benzyl	3-nitrophenyl
benzyl	4-nitrophenyl
benzyl	2-pyridyl
benzyl	2-pyridyl-N-oxide
benzyl	2-furyl
benzyl	3-indolyl
E-3-(4-hydroxyphenyl)-2-methyl-prop-2-enyl	phenyl
E-3-phenyl-2-methyl-prop-2-enyl	phenyl
E-3-[cis-(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl	phenyl
E-3-[trans-(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl	phenyl
benzyl	2-nitrobenzyl
benzyl	2-thiophenyl
hydrogen	methoxy
allyl	methoxy
benzyl	methoxy
2-cyclohexylethyl	methoxy
3-cyclohexylpropyl	methoxy
4-cyclohexylbutyl	methoxy
3-cyclopentylpropyl	methoxy
E-3-(4-methoxyphenyl)-2-methyl-prop-2-enyl	methoxy
E-3-(3,4-dimethoxyphenyl)-2-methyl-prop-2-enyl	methoxy
E-3-(4-hydroxyphenyl)-2-methyl-prop-2-enyl	methoxy
E-3-[cis-(4-hydroxycyclohexyl)]-2-methyl-prop-2-enyl	methoxy
benzyl	cyclohexyl
benzyl	3,4-difluorophenyl

benzyl	(E)-2-(4-methoxyphenyl)-ethenyl
benzyl	1-hydroxy-1-cyclohexyl
benzyl	2-napthyl
benzyl	1-napthyl
(S)-alpha-methylbenzyl	phenyl
benzyl	2-hydroxy-2-tetrahydropyranyl
(R)-alpha-methylbenzyl	phenyl
benzyl	3-trifluoromethylphenyl
benzyl	3-benzyloxyphenyl
benzyl	(E)-2-*tert*-butylethenyl
benzyl	2-trifluoromethylphenyl
4-cyclohexylbutyl	phenyl
4-cyclohexylbutyl	3,4,5-trimethoxyphenyl
4-phenylbenzyl	phenyl
4-phenylbenzyl	3,4,5-trimethoxyphenyl
benzyl	3-ethoxyphenyl
3-phenoxybenzyl	3,4,5-trimethoxyphenyl
3-phenoxybenyzl	phenyl
4-phenylbutyl	3,4,5-trimethoxyphenyl
4-phenylbutyl	phenyl
benzyl	3-(3-propenyloxy)phenyl
benzyl	3-(2-propoxy)phenyl
benzyl	1-methylpropyl
2-phenylethyl	phenyl
6-phenylhexyl	phenyl
5-phenylpentyl	3,4,5-trimethoxyphenyl
6-phenylhexyl	3,4,5-trimethoxyphenyl
6-cyclohexylhexyl	3,4,5-trimethoxyphenyl
4-phenoxybenzyl	3,4,5-trimethoxyphenyl
5-cyclohexylpentyl	3,4,5-trimethoxyphenyl
benzyl	3-(1-butoxy)phenyl
4-phenylbutyl	3-(2-propoxy)phenyl

4-(4-iodophenyl)butyl	3,4,5-trimethoxyphenyl
4-iodobenzyl	3,4,5-trimethoxyphenyl
2-(2-napthyl)ethyl	3,4,5-trimethoxyphenyl
2-(1-napthyl)ethyl	3,4,5-trimethoxyphenyl
4-phenylbutyl	4-iodophenyl
4-phenylbutyl	3-iodophenyl
3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(3-indolyl)propyl	3,4,5-trimethoxyphenyl
4-(4-methoxyphenyl)butyl	3,4,5-trimethoxyphenyl
4-phenylbut-2-enyl	3,4,5-trimethoxyphenyl
4-phenylbut-3-enyl	3,4,5-trimethoxyphenyl
4-(4-allocaminophenyl)propyl	3,4,5-trimethoxyphenyl
4-phenylpropyl	1-cyclohexenyl
4-(4-methoxyphenyl)but-3-enyl	3,4,5-trimethoxyphenyl
4-phenylpropyl	1-fluoro-1-cyclohexyl
4-phenylpropyl	3-butoxyphenyl
3-[3-(N-formylindolyl)]propyl	3,4,5-trimethoxyphenyl
4-(3-indolyl)butyl	3,4,5-trimethoxyphenyl
4-phenylbutyl	benzyl
4-phenylbutyl	3-biphenyl
4-phenylbutyl	4-*tert*-butylphenyl
4-phenylbutyl	cyclohexyl
4-phenylbutyl	cyclohexylmethyl
4-phenylbutyl	3,4-methylenedioxyphenyl
4-phenylbutyl	4-tetrahydropyranyl
4-phenylbutyl	3-cyclohexyl-4-methoxy-phenyl
4-phenylbutyl	4-(4-methoxybenzyloxy-methyl)-2-furyl
4-phenylbutyl	*tert*-butyl
4-phenylbutyl	ethyl
3-(N-benzimidazolyl)propyl	3,4,5-trimethoxyphenyl
3-(N-purinyl)propyl	3,4,5-trimethoxyphenyl
(S,S)-2-methyl-3-hydroxy-4-phenylpropyl	3,4,5-trimethoxyphenyl

Table 8



B	D	X
3-phenylpropyl	3-(3-pyridyl)propyl	phenyl
3-phenylpropyl	3-(2-pyridyl)propyl	phenyl
3-phenylpropyl	2-(4-methoxyphenyl)ethyl	phenyl
3-phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	2-(3-pyridyl)	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(2-pyridyl)	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(4-methoxyphenyl)propyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(3-pyridyl)propyl	3-*iso*-propoxyphenyl
3-(pyridin-2-yl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenoxyphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
phenyl	3-phenoxyphenyl	3,4,5-trimethoxyphenyl
phenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-(pyridin-3-yl)ethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
E-3-[trans-(4-hydroxycyclo-hexyl)]-2-methyl-eth-2-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
benzyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
benzyl	3-(3-indolyl)propyl	3,4,5-trimethoxyphenyl
2-phenylethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-(4-methoxyphenyl)ethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-(4-methoxyphenyl)ethyl	3-phenylpropyl	phenyl
3-(N-benzimidazolyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
benzyl	2-phenylethyl	3,4,5-trimethoxyphenyl

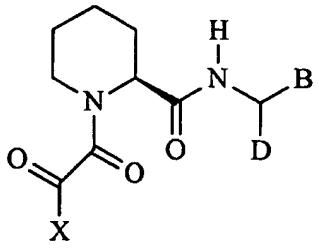
3-(4-methoxyphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(N-(7-azaindolyl)-propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(N-purinyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(4-hydroxymethylphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(pyridin-3-yl)propyl	3-phenylpropyl	3-benzyloxyphenyl
3-(pyridin-3-yl)propyl	3-phenylpropyl	3-allyloxyphenyl
3-(pyridin-3-yl)propyl	3-phenylpropyl	3-isopropoxyphenyl
3-(thiophen-2-yl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(4-carboxyphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenylbutyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-hydroxymethylphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-allyloxyphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(3-hydroxymethylphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(3-carboxyphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-hydroxymethylphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-hydroxyphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
pyridin-3-yl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(thiophen-2-yl)propyl	4-phenylpropyl	3,4,5-trimethoxyphenyl
5-phenylpentyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxypropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-N,N-dimethylamincarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
4-allyloxybutyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxyprop-1-ynyl	3-phenylpropyl	3,4,5-trimethoxyphenyl

3-[4-(piperidine-1-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
5-allyloxynonyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
methyl	3,5-bis(benzyloxy)phenyl	3,4,5-trimethoxyphenyl
2-allyloxyethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxy-(E)-prop-1-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
dec-9-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N-benzylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(thiomorpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(morpholine-4-carbonyl)phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(1-methylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(1-benzylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(N-benzylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N-pyridin-2-ylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
pyridin-3-yl	3-(pyridin-3-yl)propyl	3,4,5-trimethoxyphenyl
prop-2-enyl	3,4-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
pyridin-3-yl	3-(pyridin-4-yl-methoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(pyridin-4-yl-	3,4,5-trimethoxyphenyl

	methoxy)phenyl	
3-phenylpropyl	3,4-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,4-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	2,3,4-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(morpholine-4-carbonyl)-4-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,4,5-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3,4,5-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,5-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
ethyl	3,4,5-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,4,5-tris-(pyrazin-2-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
ethenyl	3,4,5-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
3-allyloxypropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N,N-dimethylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
4-allyloxybutyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxyprop-1-ynyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(piperidine-1-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
5-allyloxynonyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
methyl	3,5-bis(benzyloxy)phenyl	3,4,5-trimethoxyphenyl

2-allyloxyethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxy-(E)-prop-1-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
dec-9-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N-benzylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(thiomorpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(morpholine-4-carbonyl)phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(1-methylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(1-benzylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(N-benzylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
propyl	3,4,5-tris-(pyridin-4-ylmethyoxy)phenyl	3,4,5-trimethoxyphenyl
2-isopropoxy-3,4-bis-(pyridin-4-ylmethoxy)phenyl	methyl	3,4,5-trimethoxyphenyl
benzyloxymethyl	benzyloxyphenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	phenyl	3-benzyloxy-4-methoxyphenyl

Table 9



B	D	X
3-phenylpropyl	3-(3-pyridyl)propyl	phenyl
3-phenylpropyl	3-(2-pyridyl)propyl	phenyl
3-phenylpropyl	2-(4-methoxyphenyl)ethyl	phenyl
3-phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	2-(3-pyridyl)	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(2-pyridyl)	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(4-methoxyphenyl)propyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(3-pyridyl)propyl	3-*iso*-propoxyphenyl
3-(pyridin-2-yl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenoxyphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
phenyl	3-phenoxyphenyl	3,4,5-trimethoxyphenyl
phenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-(pyridin-3-yl)ethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
E-3-[trans-(4-hydroxycyclo-hexyl)]-2-methyl-eth-2-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
benzyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
benzyl	3-(3-indolyl)propyl	3,4,5-trimethoxyphenyl
2-phenylethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-(4-methoxyphenyl)ethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-(4-methoxyphenyl)ethyl	3-phenylpropyl	phenyl
3-(N-benzimidazolyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
benzyl	2-phenylethyl	3,4,5-trimethoxyphenyl
3-(4-methoxyphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(N-(7-azaindolyl)-propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(N-purinyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(4-hydroxymethylphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(pyridin-3-yl)propyl	3-phenylpropyl	3-benzyloxyphenyl
3-(pyridin-3-yl)propyl	3-phenylpropyl	3-allyloxyphenyl

3-(pyridin-3-yl)propyl	3-phenylpropyl	3-isopropoxyphenyl
3-(thiophen-2-yl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(4-carboxyphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-phenylbutyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-hydroxymethylphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-allyloxyphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(3-hydroxymethylphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(3-carboxyphenyl)propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-hydroxymethylphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
2-hydroxyphenyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
pyridin-3-yl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(thiophen-2-yl)propyl	4-phenylpropyl	3,4,5-trimethoxyphenyl
5-phenylpentyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxypropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-N,N-dimethylamincarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
4-allyloxybutyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxyprop-1-ynyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(piperidine-1-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
5-allyloxynonyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
methyl	3,5-bis(benzyloxy)phenyl	3,4,5-trimethoxyphenyl
2-allyloxyethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxy-(E)-prop-1-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
dec-9-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N-	3-phenylpropyl	3,4,5-trimethoxyphenyl

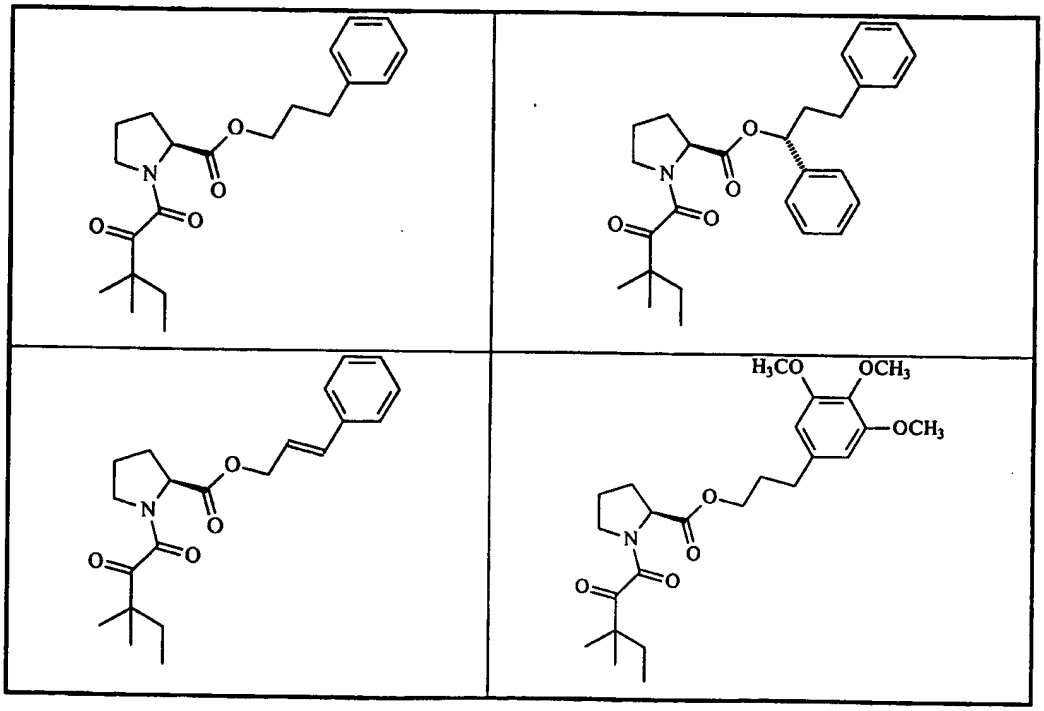
benzylaminecarbonyl)phenyl] propyl		
3-[4-(thiomorpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-(morpholine-4-carbonyl)phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(1-methylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(1-benzylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(N-benzylaminecarbonyl)phenyl] propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N-pyridin-2-ylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
pyridin-3-yl	3-(pyridin-3-yl)propyl	3,4,5-trimethoxyphenyl
prop-2-enyl	3,4-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
pyridin-3-yl	3-(pyridin-4-yl-methoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(pyridin-4-yl-methoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3,4-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,4-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	2,3,4-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	3-(morpholine-4-carbonyl)-4-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,4,5-tris-(pyridin-4-	3,4,5-trimethoxyphenyl

	ylmethoxy)phenyl	
3-phenylpropyl	3,4,5-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,5-bis-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
ethyl	3,4,5-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
methyl	3,4,5-tris-(pyrazin-2-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
ethenyl	3,4,5-tris-(pyridin-4-ylmethoxy)phenyl	3,4,5-trimethoxyphenyl
3-allyloxypropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N,N-dimethylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
4-allyloxybutyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxyprop-1-ynyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(piperidine-1-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
5-allyloxynonyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
methyl	3,5-bis(benzyloxy)phenyl	3,4,5-trimethoxyphenyl
2-allyloxyethyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-allyloxy-(E)-prop-1-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(morpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
dec-9-enyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(N-benzylaminecarbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(thiomorpholine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl

3-(morpholine-4-carbonyl)phenylpropyl	3-phenylpropyl	3,4,5-trimethoxyphenyl

3-[4-(1-methylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[4-(1-benzylpiperazine-4-carbonyl)phenyl]propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
3-[3-(N-benzylaminecarbonyl)phenyl] propyl	3-phenylpropyl	3,4,5-trimethoxyphenyl
propyl	3,4,5-tris-(pyridin-4-ylmethyoxy)phenyl	3,4,5-trimethoxyphenyl
2-isopropoxy-3,4-bis-(pyridin-4-ylmethoxy)phenyl	methyl	3,4,5-trimethoxyphenyl
benzyloxymethyl	benzyloxyphenyl	3,4,5-trimethoxyphenyl
3-phenylpropyl	phenyl	3-benzyloxy-4-methoxyphenyl

Table 10



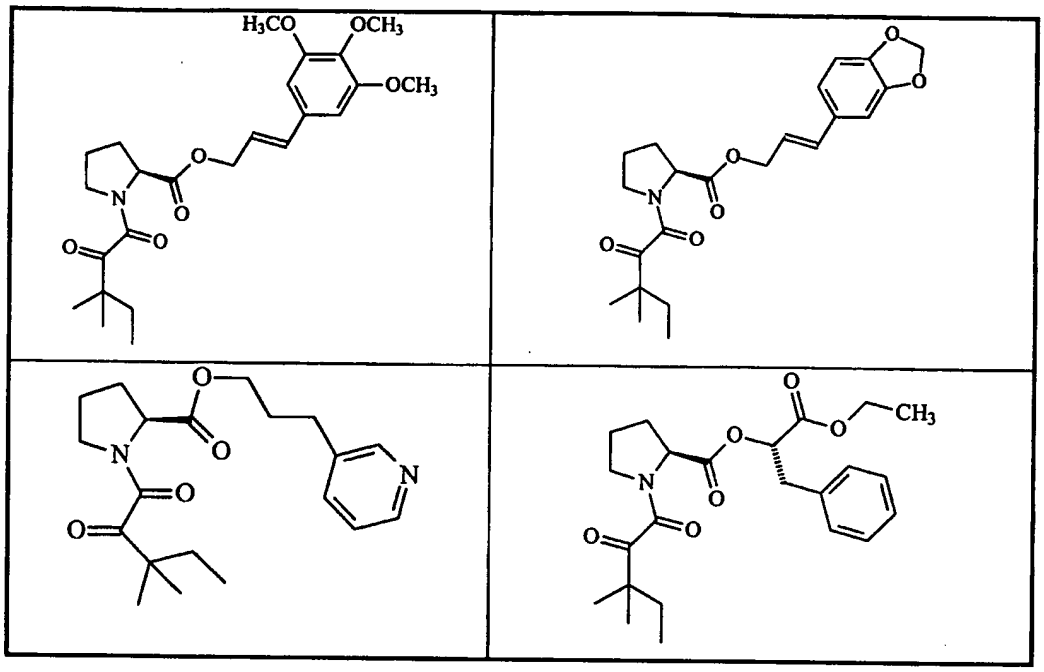
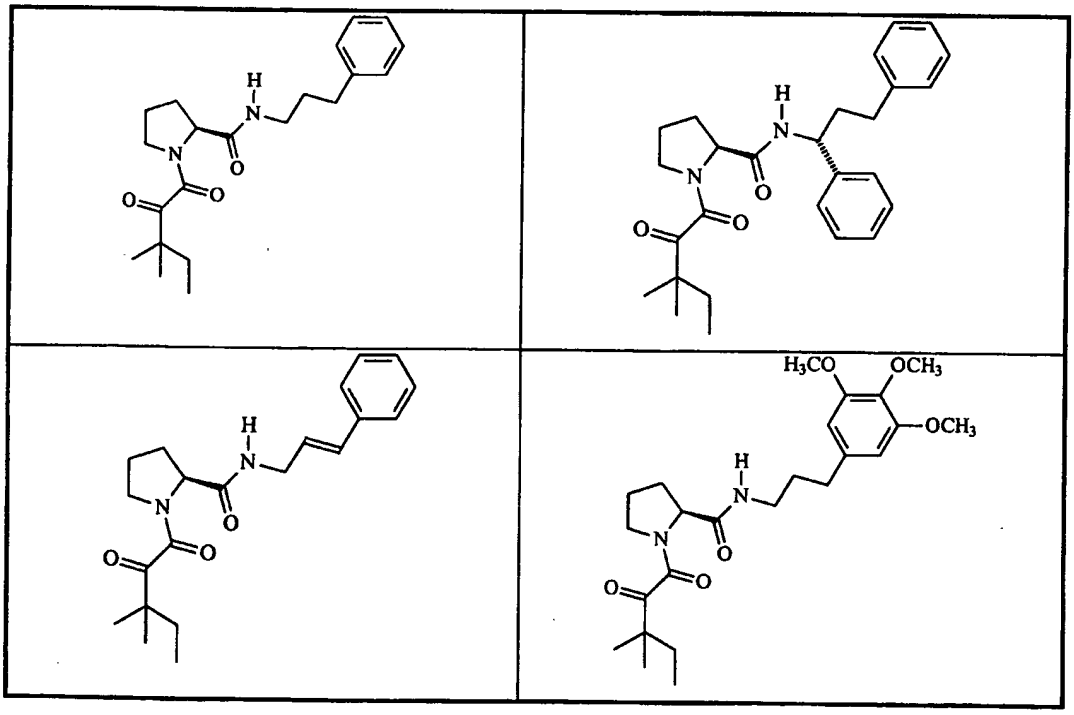


Table 11



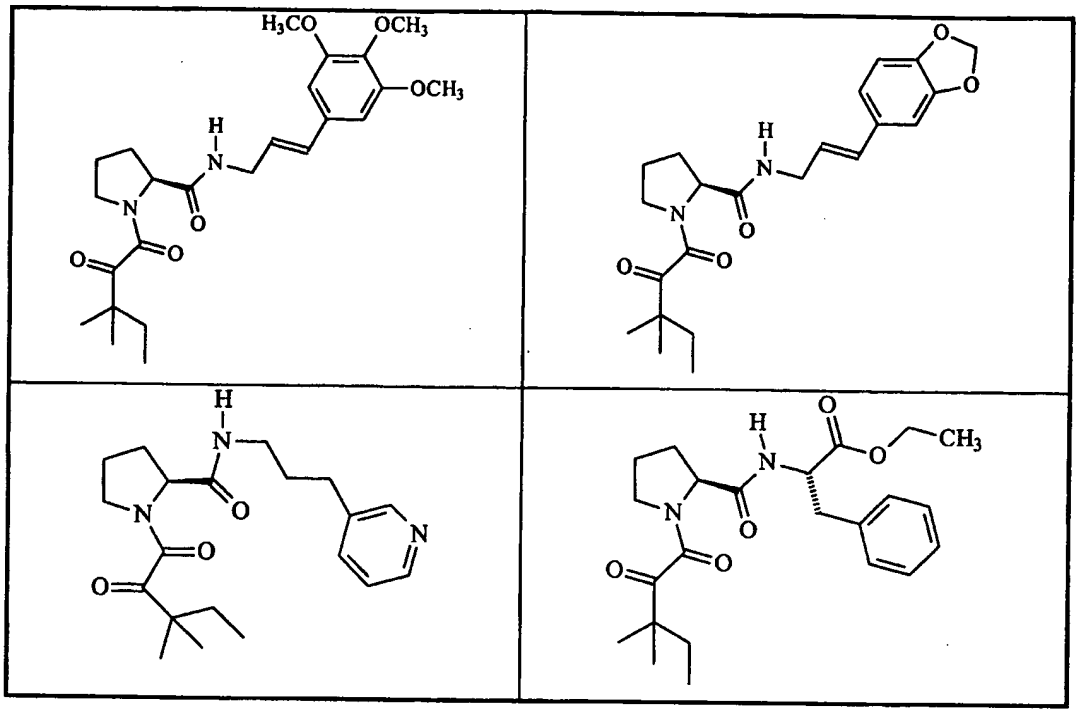
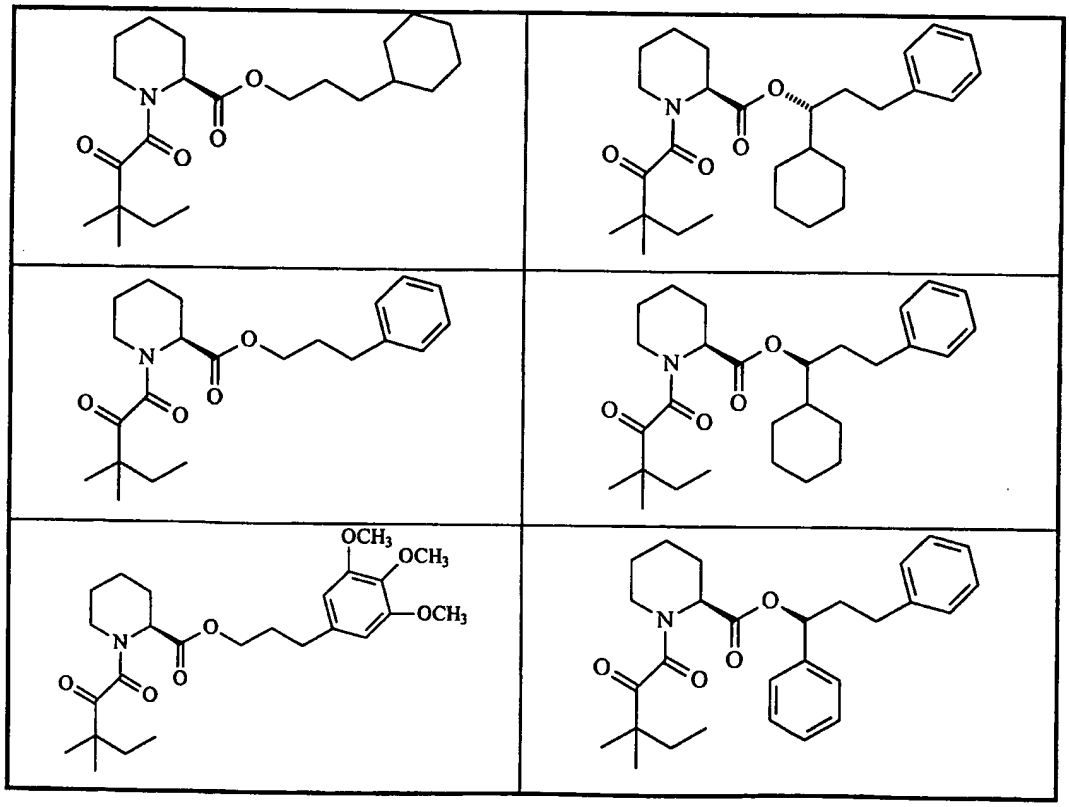


Table 12



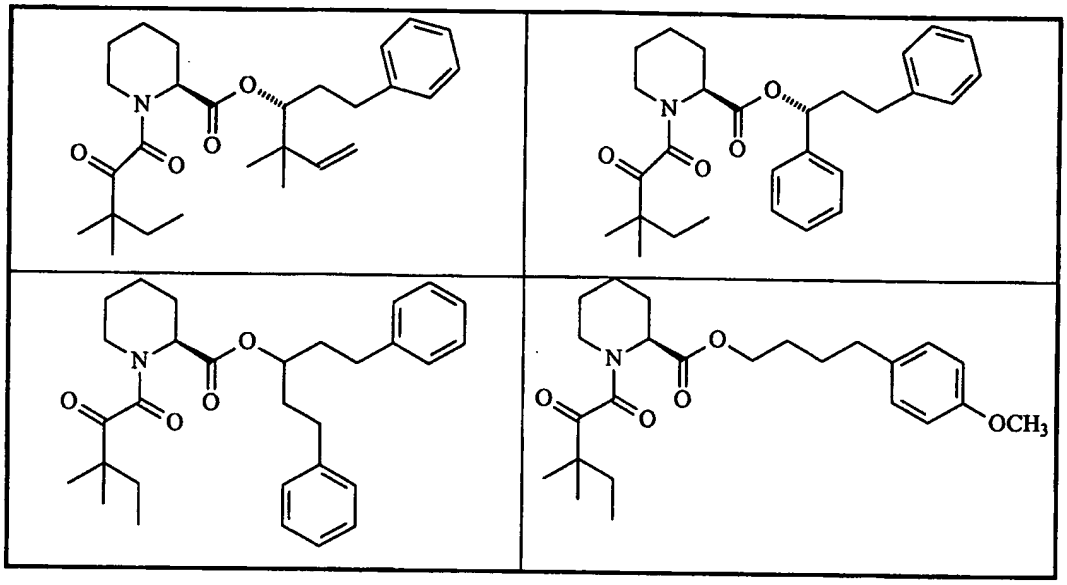
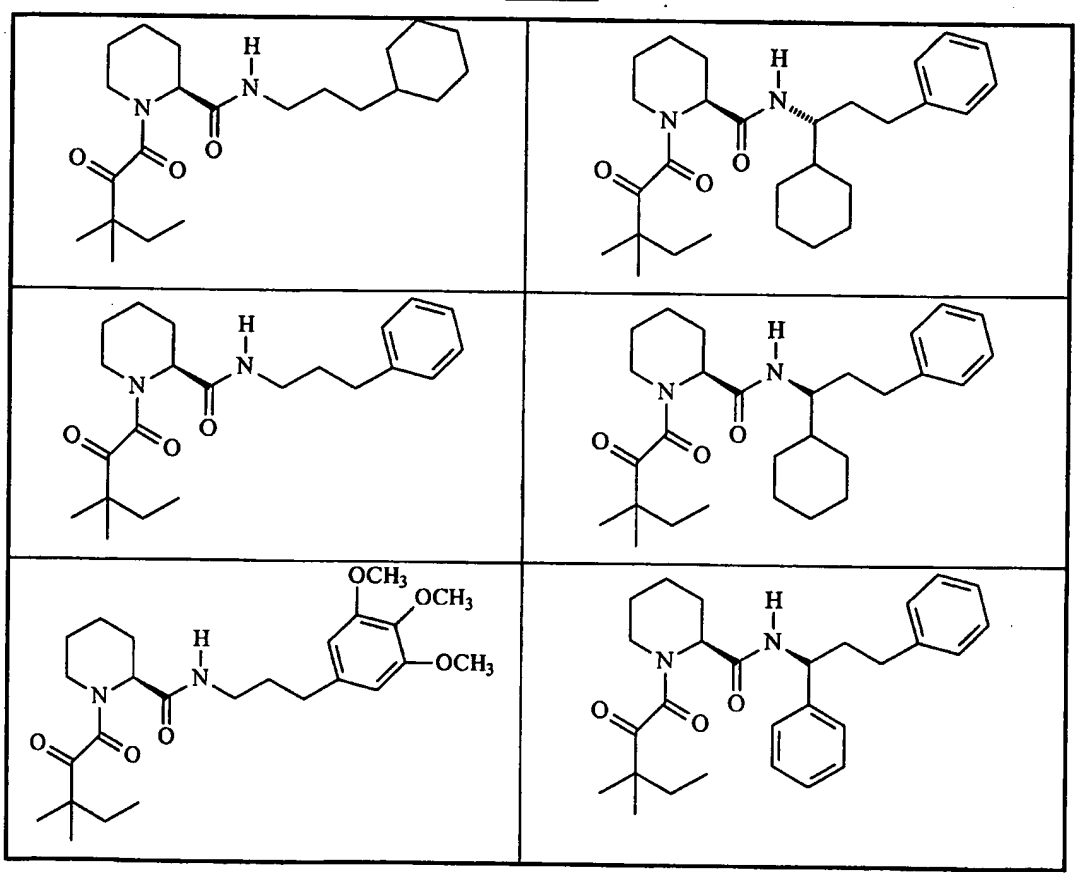


Table 13



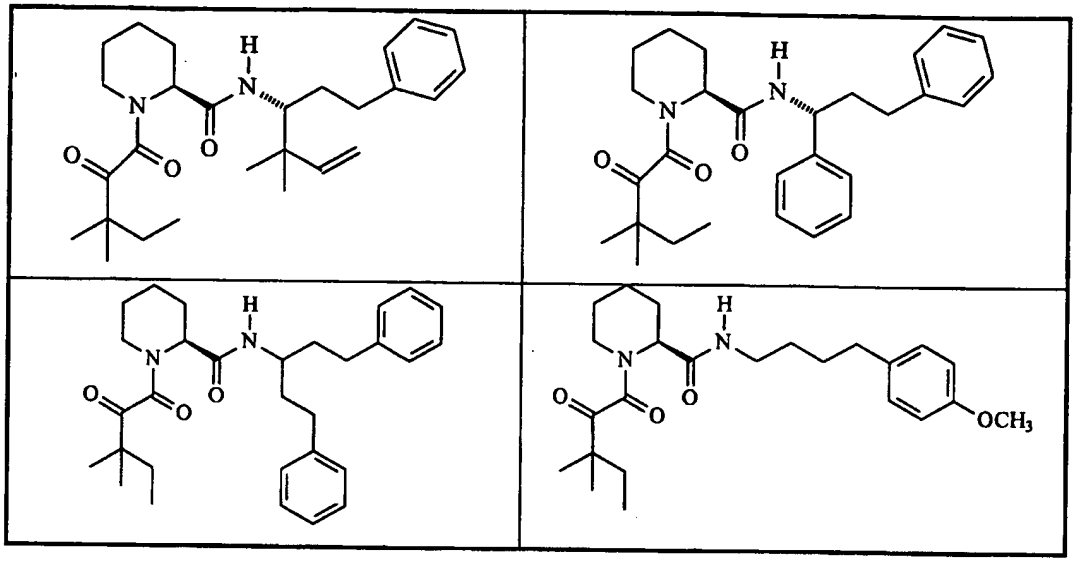
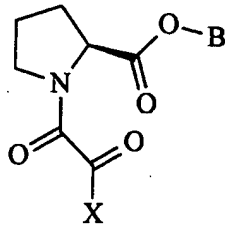
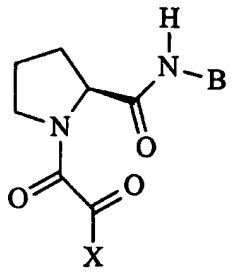


Table 14



B	X
benzyl	phenyl
tert-butyl	2-furyl
tert-butyl	methoxy
benzyl	ethyl
benzyl	3-methoxyphenyl
benzyl	2-pyridyl

Table 15



B	X
benzyl	phenyl
tert-butyl	2-furyl
tert-butyl	methoxy
benzyl	ethyl
benzyl	3-methoxyphenyl
benzyl	2-pyridyl

Analytical Methods

The present invention relates to methods of treating hair loss by administering a compound having a structure as described herein. Of such compounds, the preferred compounds are non-immunosuppressive. Compounds (test compounds) may be tested for their ability to induce anagen and their immunosuppressive activity (or lack thereof) using the following methods. Alternatively, other methods well-known in the art may be used (but with the term "non-immunosuppressive" being defined according to the method disclosed herein below).

Telogen Conversion Assay:

The Telogen Conversion Assay measures the potential of a test compound to convert mice in the resting stage of the hair growth cycle ("telogen"), to the growth stage of the hair growth cycle ("anagen").

Without intending to be limited by theory, there are three principal phases of the hair growth cycle: anagen, catagen, and telogen. It is believed that there is a longer telogen period in C3H mice (Harlan Sprague Dawley, Inc., Indianapolis, IN) from approximately 40 days of age until about 75 days of age, when hair growth is synchronized. It is believed that after 75 days of age, hair growth is no longer synchronized. Wherein about 40 day-old mice with dark fur (brown or black) are used in hair growth experiments, melanogenesis occurs along with hair (fur) growth wherein the topical application of hair growth promoters are evaluated. The Telogen Conversion

Assay herein below is used to screen compounds for potential hair growth by measuring melanogenesis.

Three groups of 44 day-old C3H mice are utilized: a vehicle control group, a positive control group, and a test compound group, wherein the test compound group is administered a compound used in the method of the present invention. The length of the assay is at least 19 days with 15 treatment days (wherein the treatment days occur Mondays through Fridays). Day 1 is the first day of treatment. Most studies will end on Day 19, but a few may be carried out to Day 24 if the melanogenesis response looks positive, but occurs slowly. A typical study design is shown in Table 16 below:

Table 16

Group #	Animal #	Compound	Concentration	Application volume	Length of Study
1	1 - 10	Test Compound	5% in vehicle**	400 µL topical	19 or 24 days
2	11 - 20	Cyclosporin A	0.19% in vehicle**	400 µL topical	19 or 24 days
3	21 - 30	Vehicle**	N/A	400 µL topical	19 or 24 days

**The vehicle is 60% ethanol, 20% propylene glycol, and 20% dimethyl isosorbide (commercially available from Sigma Chemical Co., St. Louis, MO).

The mice are treated topically Monday through Friday on their lower back (base of tail to the lower rib). A pipettor and tip are used to deliver 400 µL to each mouse's back. The 400 µL application is applied slowly while moving hair on the mouse to allow the application to reach the skin.

While each treatment is being applied to the mouse topically, a visual grade of from 0 to 4 will be given to the skin color in the application area of each animal. As the mice convert from telogen to anagen their skin color will become more bluish-black. As indicated in Table 17, the grades 0 to 4 represent the following visual observations as the skin progresses from white to bluish-black:

Table 17

Visual Observation	Grade
Whitish Skin Color	0
Skin is light gray (indication of initiation of anagen)	1
Appearance of Blue Spots	2

Blue Spots are aggregating to form one large blue area	3
Skin is dark blue (almost black) with color covering majority of treatment area (indication of mouse in full anagen)	4

Immunosuppression Assay:

The immunosuppression assay herein predicts the immunosuppressive activity of a compound used in the method of the present invention. The assay is performed as follows:

Spleens are excised from euthanized (CO_2 asphyxiation) adult male C3H mice ranging in age from seven to sixteen weeks old (live mice commercially available from Harlan Sprague Dawley, Inc., Indianapolis, IN). The spleens are placed immediately in cold Hanks Balanced Salt Solution (HBSS, commercially available from Gibco-BRL, Gaithersburg, MD). The spleens are then ground up between frosted glass slides and filtered through a sterile screen to remove tissue debris. The resulting cell suspension is underlayed with an equal volume of Ficoll-Paque Plus (commercially available from Pharmacia Biotech, Piscataway, NJ) and centrifuged at 400 x g for approximately forty minutes at 20 °C in order to collect the splenocytes. The splenocytes are collected from the interface using a disposable pipet and are washed twice with HBSS, followed by centrifugation at 100 x g for ten min at 20 °C. Splenocytes are resuspended in five to ten mL of cell culture media consisting of phenol red-free RPMI 1640 (culture media commercially available from Gibco-BRL) containing 10% heat-inactivated fetal bovine serum (Gibco-BRL), penicillin (50 U/mL), streptomycin (100 µg/mL), L-glutamine (2 mM), 2-mercaptoethanol (10^{-5} M), and N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (10 mM). The cells are counted and checked for viability using, for example, trypan blue. Splenocytes are resuspended in medium at 10^6 cells/mL and pipetted into 96 well round bottom plates at 10^5 cells/well. Splenocytes are activated by addition of 50 µL/well of conconavalin A (final assay concentration = 5 µg/ml) in the presence or absence of a test compound. Test compounds are made up as stock solutions in methyl sulfoxide (DMSO), then diluted in medium and 50 µL/well added, such that the final concentration of DMSO in the assay is below 0.05%. The plates are incubated at 37 °C with 5% CO_2 for 48 hours. After 48 hours, the cells are pulsed with 1 µCi/well of methyl-^{3}H-thymidine (commercially available from Amersham, Buckinghamshire, England) and incubated an additional 24 hours.

After 24 hours, the cells are harvested onto GF/C filter plates (commercially available from Packard, Downers Grove, IL), solubilized in Microscint 20 (Packard), and counted on a

TopCount microplate scintillation and luminescence plate counter (Packard). Activity is measured as a percentage of control activity in the absence of test compound and plotted *versus* test compound concentration. The data are fit to a 4-parameter curve fit (Sigmaplot) and IC_{50} values are calculated. As used herein, test compounds are considered non-immunosuppressive if, by using this method, the ratio of (cyclosporin A IC_{50}/test compound IC_{50}) x 100 is less than or equal to 0.02, *i.e.*, a non-immunosuppressive test compound has ≤ 2% of the immunosuppressive activity of cyclosporin A.

Cell viability is assessed using the MTT (3-[4,5-dimethyl-thiazoyl-2-yl]2,5-diphenyl-tetrazolium bromide) dye assay as described by Nelson et al., Journal of Immunology, Vol. 150, No. 6, pp. 2139 - 2147 (1993), with the exception that the assay is carried out in serum-free, phenol red-free RPMI 1640 and the dye is solubilized in 100 μL/well DMSO and read at an OD of 540 nm with a background correction at 650 nm on a SpectraMax Plus microplate reader (Molecular Devices, Menlo Park, CA).

Methods of Making

The compounds used in the methods of the present invention are prepared according to methods which are well-known to those skilled in the art. The starting materials used in preparing the compounds are known, made by known methods, or are commercially available as a starting material.

It is recognized that the skilled artisan in the art of organic chemistry can readily carry out standard manipulations of organic compounds without further direction. Examples of such manipulations are discussed in standard texts such as J. March, Advanced Organic Chemistry, John Wiley & Sons, 1992.

The skilled artisan will readily appreciate that certain reactions are best carried out when other functionalities are masked or protected in the compound, thus increasing the yield of the reaction and / or avoiding any undesirable side reactions. Often, the skilled artisan utilizes protecting groups to accomplish such increased yields or to avoid the undesired reactions. These reactions are found in the literature and are also well within the scope of the skilled artisan. Examples of many such manipulations can be found in, for example, T. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, 1981.

The compounds of the present invention may have one or more chiral center. As a result, one may selectively prepare one optical isomer, including diastereomers and enantiomers, over another, for example by chiral starting materials, catalysts or solvents, or may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures,

mixtures of optical isomers, including diastereomers and enantiomers, or stereoisomers may be separated using known methods, such as through the use of, for example, chiral salts and chiral chromatography.

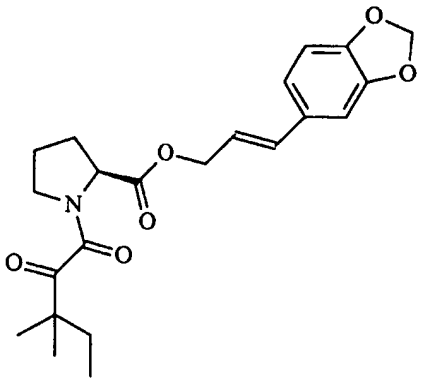
In addition, it is recognized that one optical isomer, including a diastereomer and enantiomer, or a stereoisomer, may have favorable properties over the other. Thus, when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

The following provides non-limiting examples illustrating more specifically the methods of making various compounds of the present invention.

As used herein, the following abbreviations are used:

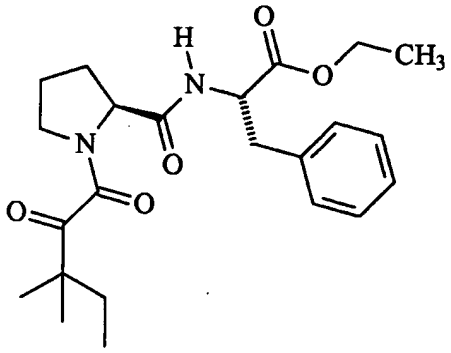
Reagent	Abbreviation
N,N - dimethylformamide	DMF
1-hydroxybenzotriazole hydrate	HOBt
tert-butoxycarbonyl	BOC
(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (commercially available from Fluka Chemical, Switzerland)	PyBOP
tetrahydrofuran	THF
N,N - diisopropylethylamine	i-Pr_2NEt or i-Pr_2EtN
trifluoroacetic acid	TFA

Example 1



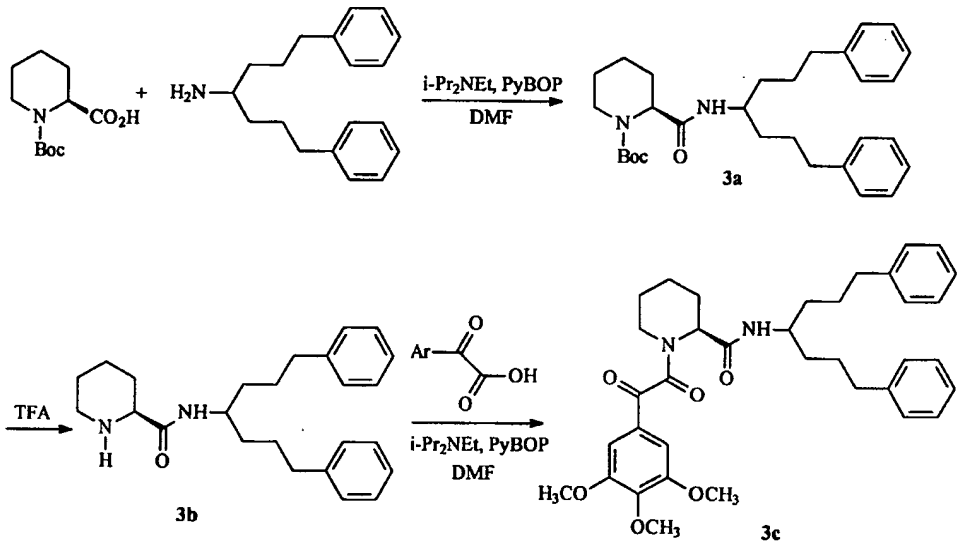
The above compound is prepared as described in U.S. Patent No. 5,614,547, Hamilton et al., assigned to Guilford Pharmaceuticals Inc., issued March 25, 1997.

Example 2



The above compound is prepared as described in U.S. Patent No. 5,614,547, Hamilton et al., assigned to Guilford Pharmaceuticals Inc., issued March 25, 1997.

Example 3



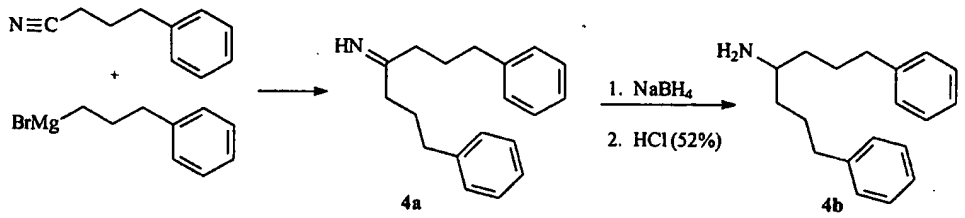
3a. (S)-(N-*tert*-Butoxycarbonyl)pipecolic acid 1,7-diphenyl-4-heptylamide: (S)-(N-tert-Butoxycarbonyl)pipecolic acid (4.7 g, 20.3 mmol) is dissolved in 200 mL of DMF. 1,7-Diphenyl-4-aminoheptane (5.44 g, 20.3 mmol) (which may be prepared as in Example 4 below) and i-Pr_2EtN (7.1 mL, 40.7 mmol) are added followed by PyBOP (10.6 g, 20.3 mmol). The reaction is stirred for 18 hours at room temperature, then poured onto ice-cold 0.1N HCl (800 mL) and extracted with ethyl acetate (800 mL). The layers are separated and the organic layer washed successively with brine (200 mL), saturated $NaHCO_3$ solution (400 mL), and brine (200

mL). The organic solution is dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the product by chromatography on silica gel affords the desired amide **3a**.

3b. (S)-Pipecolic acid 1,7-diphenyl-4-heptylamide: The amide **1a** (8.74 g, 18.3 mmol) is dissolved in 150 mL of anhydrous dichloromethane. TFA (100 mL) is added dropwise over a 5 minute period. After two hours the mixture is cooled in an ice-bath and saturated K_2CO_3 solution is added until the pH is approximately 8. The mixture is transferred to a separatory funnel containing dichloromethane (200 mL) and water (200 mL) and shaken. The organic layer is separated and washed with water (200 mL) before drying over $MgSO_4$. The mixture is filtered and concentrated *in vacuo* to afford the desired amine **3b**.

3c. (S)-N-(3',4',5'-Trimethoxyphenylglyoxyl)pipecolic acid 1,7-diphenyl-4-heptylamide: The amine **3b** (0.65 g, 1.72 mmol) is dissolved in 35 mL of anhydrous DMF. 3',4',5'-Trimethoxyphenylglyoxylic acid (0.4 g, 1.72 mmol) and i-Pr_2EtN (0.44 g, 3.43 mmol) are added followed by PyBOP (0.9 g, 1.72 mmol). The reaction is stirred for 21 hours at room temperature, then poured onto ice-cold 0.1N HCl (150 mL) and extracted with ethyl acetate (150 mL). The layers are separated and the organic layer is washed successively with brine (50 mL), saturated $NaHCO_3$ solution (150 mL) and brine (50 mL). The organic solution is dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the product by chromatography on silica gel affords the desired amide **3c**.

Example 4

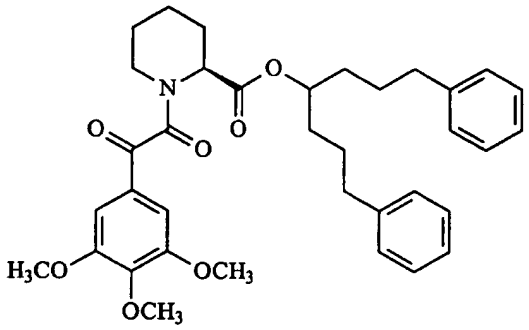


4a. Magnesium (40.2 g, 1.65 mol) and anhydrous ether (3.2 L) are combined in a reaction vessel with stirring. A solution of 1-bromo-3-phenyl propane in 1.6 L of anhydrous ether is added to an addition funnel. The bromide solution is added dropwise to the stirring reaction vessel over a 1 hour period. Upon completion of addition, the mixture stirs for 1 - 2 hours. A solution of 4-phenylbutyronitrile (160 g, 1.1 mol) in anhydrous ether (2.4 L) is placed in the

addition funnel. The solution is added to the reaction vessel over a 1 hour time period. Upon complete addition the solution is heated to reflux for 10 hours, and then stirs at room temperature for six hours.

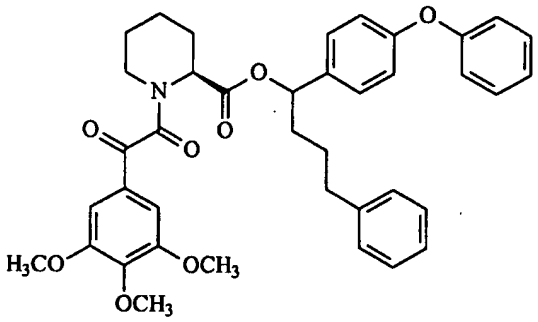
4b. 1,7-Diphenyl-4-aminoheptane: The reaction mixture of **4a** is diluted with methanol (3.2 L) using an addition funnel. Sodium borohydride (83.4 g, 2.2 mol) is added in portions. Upon complete addition the reaction is stirred at room temperature for six hours. The reaction mixture is quenched by a slow addition of water (3.2 L). The mixture is diluted with ether (3.2 L) and water (1.6 L). The ether layer is separated and the aqueous layer is extracted twice with ether (3.2 L x 2). The combined ether extracts are washed once with sodium chloride solution, dried, filtered, and concentrated *in vacuo* to give the crude product. This product is diluted in ether (1.2 L) and acidified by slow addition of 1M HCl (1.2 L). The mixture stirs for one hour and is concentrated *in vacuo*. The resulting precipitate is diluted with acetonitrile and is stirred for 16 hours. The desired 1,7-Diphenyl-4-aminoheptane is collected by filtration.

Example 5



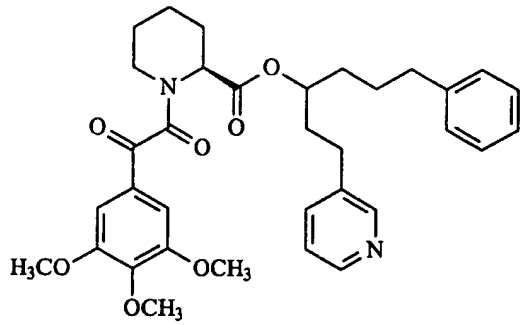
The above compound is prepared as described in U.S. Patent No. 5,620,971, Armistead et al., assigned to Vertex Pharmaceuticals Inc., issued April 15, 1997.

Example 6



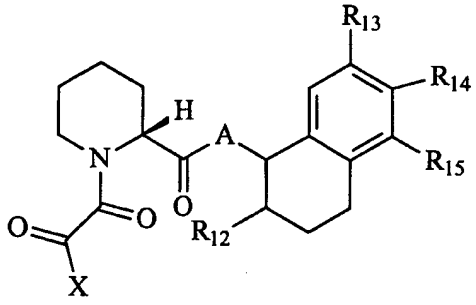
The above compound is prepared as described in U.S. Patent No. 5,620,971, Armistead et al., assigned to Vertex Pharmaceuticals Inc., issued April 15, 1997.

Example 7



The above compound is prepared as described in U.S. Patent No. 5,620,971, Armistead et al., assigned to Vertex Pharmaceuticals Inc., issued April 15, 1997.

Example 8



Compounds having the above structure may be prepared as described in U.S. Patent No. 5,726,184, Zelle, assigned to Vertex Pharmaceuticals Inc., issued March 10, 1998.

Use of the Present Compounds

The method of the present invention is performed by administration of a compound having a structure herein and a pharmaceutically-acceptable carrier.

The compounds herein may be used for the treatment of such conditions as treating hair loss in mammals, including arresting and / or reversing hair loss and promoting hair growth. Such conditions may manifest themselves in, for example, alopecia, including male pattern baldness and female pattern baldness.

While certain of the present compounds may exhibit immunosuppressive activity, the preferred compounds of the present invention are, as defined herein, non-immunosuppressive.

Preferably, in the methods of the present invention, the compounds are formulated into pharmaceutical compositions for use in treatment or prophylaxis of conditions such as the foregoing. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. (1990).

Typically, from about 5 mg to about 3000 mg, more preferably from about 5 mg to about 1000 mg, more preferably from about 10 mg to about 100 mg, of a compound having a structure as described herein is administered per day for systemic administration. It is understood that these dosage ranges are by way of example only, and that daily administration can be adjusted depending on various factors. The specific dosage of the compound to be administered, as well as the duration of treatment, and whether the treatment is topical or systemic are interdependent. The dosage and treatment regimen will also depend upon such factors as the specific compound used, the treatment indication, the efficacy of the compound, the personal attributes of the subject (such as, for example, weight, age, sex, and medical condition of the subject), compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

According to the present invention, the subject compounds are co-administered with a pharmaceutically-acceptable carrier ("carrier"). The term pharmaceutically-acceptable carrier, as used herein, means one or more compatible solid or liquid filler diluents or encapsulating substances which are suitable for administration to a mammal. The term "compatible", as used herein, means that the components of the composition are capable of being commingled with a compound of the present invention, and with each other, in a manner such that there is no interaction which would substantially reduce the efficacy of the composition under ordinary use situations. Carriers must, of course, be of sufficiently high purity and sufficiently low toxicity to render them suitable for administration to the animal, preferably mammal, being treated. The carrier can itself be inert or it can possess pharmaceutical benefits of its own.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical, nasal, ocular or parenteral administration. Of these, topical or oral administration is especially preferred. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in

the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the activity of the compound of the present invention. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references: Modern Pharmaceutics, Chapters 9 and 10, Banker & Rhodes, eds. (1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms, 2nd Ed., (1976).

Some examples of substances which can serve as pharmaceutically-acceptable carriers or components thereof are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is basically determined by the way the compound is to be administered.

In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of a compound of the present invention. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions,

suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

The pharmaceutically-acceptable carrier suitable for the preparation of unit dosage forms for oral administration are well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid and talc. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules (including time release and sustained release formulations) typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which are not critical for the purposes of the subject invention, and can be readily made by a person skilled in the art.

Orally administered compositions also include liquid solutions, emulsions, suspensions, powders, granules, elixirs, tinctures, syrups, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or

more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

The compounds of the present invention may also be topically administered. The carrier of the topical composition preferably aids penetration of the present compounds into the skin to reach the environment of the hair follicle. Topical compositions of the present invention may be in any form including, for example, solutions, creams, ointments, gels, lotions, shampoos, leave-on and rinse-out hair conditioners, milks, cleansers, moisturizers, sprays, skin patches, and the like.

Topical compositions containing the active compound can be admixed with a variety of carrier materials well known in the art, such as, for example, water, alcohols, aloe vera gel, allantoin, glycerine, vitamin A and E oils, mineral oil, propylene glycol, PPG-2 myristyl propionate, and the like.

Other materials suitable for use in topical carriers include, for example, emollients, solvents, humectants, thickeners and powders. Examples of each of these types of materials, which can be used singly or as mixtures of one or more materials, are as follows:

Emollients, such as stearyl alcohol, glyceryl monoricinoleate, glyceryl monostearate, propane-1,2-diol, butane-1,3-diol, mink oil, cetyl alcohol, *iso*-propyl isostearate, stearic acid, *iso*-butyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, cetyl palmitate, dimethylpolysiloxane, di-*n*-butyl sebacate, *iso*-propyl myristate, *iso*-propyl palmitate, *iso*-propyl stearate, butyl stearate, polythylene glycol, triethylene glycol, lanolin, sesame oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum, mineral oil, butyl myristate, isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, and myristyl myristate; propellants, such as propane, butane, *iso*-butane, dimethyl ether, carbon dioxide, and nitrous oxide; solvents, such as ethyl alcohol, methylene chloride, *iso*-propanol, castor oil, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran; humectants, such as glycerin, sorbitol, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, and gelatin; and powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silicon dioxide, sodium polyacrylate, tetra alkyl ammonium smectites, trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, and ethylene glycol monostearate.

The compounds used in the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines. A preferred formulation for topical delivery of the present compounds utilizes liposomes such as described in Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", S.T.P. Pharma Sciences, Vol. 3, pp. 404 - 407 (1993), Wallach and Philippot, "New Type of Lipid Vesicle: Novasome®", Liposome Technology, Vol. 1, pp. 141 - 156 (1993), and Wallach, U.S. Patent No. 4,911,928, assigned to Micro-Pak, Inc., issued March 27, 1990.

The compounds of the present invention may also be administered by iontophoresis. See, e.g., www.unipr.it/arpa/dipfarm/erasmus/erasm14.html, Banga et al., "Hydrogel-based Iontotherapeutic Delivery Devices for Transdermal Delivery of Peptide/Protein Drugs", Pharm. Res., Vol. 10 (5), pp. 697-702 (1993), Ferry L.L., "Theoretical Model of Iontophoresis Utilized in Transdermal Drug Delivery", Pharmaceutical Acta Helvetiae, Vol 70, pp. 279-287 (1995), Gangarosa et al., "Modern Iontophoresis for Local Drug Delivery", Int. J. Pharm, Vol. 123, pp. 159-171 (1995), Green et al., "Iontophoretic Delivery of a Series of Tripeptides Across the Skin *in vitro*", Pharm. Res., Vol 8, pp. 1121-1127 (1991), Jadoul et al., "Quantification and Localization of Fentanyl and TRH Delivered by Iontophoresis in the Skin", Int. J. Pharm., Vol. 120, pp. 221-8 (1995), O'Brien et al., "An Updated Review of its Antiviral Activity, Pharmacokinetic Properties and Therapeutic Efficacy", Drugs, Vol. 37, pp. 233-309 (1989), Parry et al., "Acyclovir Biovailability in Human Skin", J. Invest. Dermatol., Vol. 98 (6), pp. 856-63 (1992), Santi et al., "Drug Reservoir Composition and Transport of Salmon Calcitonin in Transdermal Iontophoresis", Pharm. Res., Vol 14 (1), pp. 63-66 (1997), Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: I. pH and Ionic Strength", J. Control. Release, Vol. 38, pp. 159-165 (1996), Santi et al., "Reverse Iontophoresis - Parameters Determining Electroosmotic Flow: II. Electrode Chamber Formulation", J. Control. Release, Vol. 42, pp. 29-36 (1996), Rao et al., "Reverse Iontophoresis: Noninvasive Glucose Monitoring *in vivo* in Humans", Pharm. Res., Vol. 12 (12), pp. 1869-1873 (1995), Thysman et al., "Human Calcitonin Delivery in Rats by Iontophoresis", J. Pharm. Pharmacol., Vol. 46, pp. 725-730 (1994), Volpato et al., "Iontophoresis Enhances the Transport of Acyclovir through Nude Mouse Skin by Electrorepulsion and Electroosmosis", Pharm. Res., Vol. 12 (11), pp. 1623-1627 (1995).

The compositions of the present invention may also optionally comprise an activity enhancer. The activity enhancer can be chosen from a wide variety of molecules which can function in different ways to enhance hair growth effects of a compound of the present invention.

Particular classes of activity enhancers include other hair growth stimulants and penetration enhancers.

Additional hair growth stimulants can be chosen from a wide variety of molecules which can function in different ways to enhance the hair growth effects of a compound of the present invention. These optional other hair growth stimulants, when present, are typically employed in the compositions herein at a level ranging from about 0.01% to about 15%, preferably from about 0.1% to about 10%, most preferably from about 0.5% to about 5% by weight of the composition.

Vasodilators such as potassium channel agonists including, for example, minoxidil and minoxidil derivatives such as aminexil and such as those described in U.S. Patent 3,382,247, U.S. Patent 5,756,092, issued May 26, 1998, U.S. Patent 5,772,990, issued June 30, 1998, U.S. Patent 5,760,043, issued June 2, 1998, U.S. Patent 328,914, issued July 12, 1994, U.S. Patent 5,466,694, issued November 14, 1995, 5,438,058, issued August 1, 1995, and U.S. Patent 4,973,474, issued November 27, 1990, (all of which are herein incorporated by reference), and cromakalin and diazoxide can be used as an additional hair growth stimulant in the compositions herein.

One suitable class of additional hair growth stimulant for use herein are antiandrogens. Examples of suitable antiandrogens may include, but are not limited 5-α-reductase inhibitors such as finasteride and those described in U.S. Patent 5,516,779, issued May 14, 1996 (herein incorporated by reference) and in Nane et al., Cancer Research 58, "Effects of Some Novel Inhibitors of C17,20-Lyase and 5α-Reductase *in vitro* and *in vivo* and Their Potential Role in the Treatment of Prostate Cancer," as well as cyproterone acetate, azelaic acid and its derivatives and those compounds described in U.S. Patent 5,480,913, issued January 2, 1996, flutamide, and those described in U.S. Patents 5,411,981, issued May 2, 1995, U.S. Patent5,565,467, issued October 15, 1996 and U.S. Patent 4,910,226, issued March 20, 1990, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are immunosuppressants or non-immunosuppressants such as 1) cyclosporin and cyclosporin analogs including those described in U.S. Provisional Patent Application No. 60/122,925, Fulmer et al., filed March 5, 1999, herein incorporated by reference, and 2) FK506 analogs such as those described in U.S. Provisional Patent Application No. 60/147,279, Degenhardt et al., filed August 5, 1999; U.S. Provisional Patent Application No. 60/147,313, Degenhardt et al., filed August 5, 1999; U.S. Provisional Patent Application No. 60/147,280, Degenhardt et al., filed August 5, 1999; U.S. Provisional Patent Application No. 60/147,278, Degenhardt et al., filed August 5, 1999; and U.S.

Provisional Patent Application No. 60/147,276, Eickhoff et al., filed August 5, 1999; all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are antimicrobials such as selenium sulfide, ketoconazole, triclocarbon, triclosan, zinc pyrithione, itraconazole, asiatic acid, hinokitiol, mipirocin and those described in EPA 0,680,745 (herein incorporated by reference), clinacycin hydrochloride, benzoyl peroxide, benzyl peroxide and minocyclin.

Anti-inflammatories can also be incorporated into the compositions herein as an optional hair growth stimulant. Examples of suitable anti-inflammatories may include glucocorticoids such as hydrocortisone, mometasone furoate and prednisolone, nonsteroidal anti-inflammatories including cyclooxygenase or lipoxygenase inhibitors such as those described in U.S. Patent 5,756,092, and benzydamine, salicylic acid, and those compounds described in EPA 0,770,399, published May 2, 1997, WO 94/06434, published March 31, 1994, and FR 2,268,523, published November 21, 1975, all of which are herein incorporated by reference.

Another suitable class of optional hair growth stimulants are thyroid hormones and derivatives and analogs thereof. Examples of suitable thyroid hormones for use herein may include triiodothyrionine. Examples of thyroid hormone analogs which may be suitable for use herein include those described in U.S. Provisional Patent Application No. 60/136,996, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,024, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,022, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,023, Zhang et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,052, Youngquist et al., filed June 1, 1999, U.S. Provisional Patent Application No. 60/137,063, Youngquist et al., filed June 1, 1999, and U.S. Provisional Patent Application No. 60/136,958, Youngquist et al., filed June 1, 1999.

Prostaglandin agonists or antagonists can also be used as optional hair growth stimulants in the compositions herein. Examples of suitable prostaglandins agonists or antagonists include latanoprost and those described in WO 98/33497, Johnstone, published August 6, 1998, WO 95/11003, Stjernschantz, published April 27, 1995, JP 97-100091, Ueno and JP 96-134242, Nakamura.

Another class of optional hair growth stimulants for use herein are retinoids. Suitable retinoids may include isotretinoin, acitretin, and tazarotene.

Another class of optional hair growth stimulants for use herein are triterpenes such as, for example, those disclosed in Bradbury et al., U.S. Patent Application Serial No. 09/353,408, "Method for Regulating Hair Growth", filed July 15, 1999 and Bradbury et al., U.S. Patent

Application Serial No. 09/353,409, "Compositions Which Contain Triterpenes for Regulating Hair Growth", filed July 15, 1999, each incorporated by reference in their entirety.

Other classes of optional hair growth stimulants for use herein include flavinoids, ascomycin derivatives and analogs, histamine antagonists such as diphenhydramine hydrochloride, other triterpenes such as oleanolic acid and ursolic acid and those described in U.S. Patent 5,529,769, JP 10017431, WO 95/35103, U.S. Patent 5,468,888, JP 09067253, WO 92/09262, JP 62093215, U.S. Patent 5,631,282, U.S. Patent 5,679,705, JP 08193094, saponins such as those described in EP 0,558,509 to Bonte et al., published September 8, 1993 and WO 97/01346 to Bonte et al, published January 16, 1997 (both of which are herein incorporated by reference in their entirety), proteoglycanase or glycosaminoglycanase inhibitors such as those described in U.S. Patents 5,015,470, issued May 14, 1991, U.S. Patent 5,300,284, issued April 5, 1994 and U.S. Patent 5,185,325, issued February 9, 1993 (all of which are herein incorporated in their entirety by reference) estrogen agonists and antagonists, pseudoterins, cytokine and growth factor promotors, analogs or inhibitors such as interleukin1 inhibitors, interleukin-6 inhibitors, interleukin-10 promotors, and tumor necrosis factor inhibitors, vitamins such as vitamin D analogs and parathyroid hormone antagonists, Vitamin B12 analogs and panthenol, interfuron agonists and antagonists, hydroxyacids such as those described in U.S. Patent 5,550,158, benzophenones, and hydantoin anticonvulsants such as phenytoin.

Other additional hair growth stimulants are described in detail in, for example, JP 09-157,139 to Tsuji et al., published June 17, 1997; EP 0277455 A1 to Mirabeau, published August 10, 1988; WO 97/05887 to Cabo Soler et al., published February 20, 1997; WO 92/16186 to Bonte et al., published March 13, 1992; JP 62-93215 to Okazaki et al., published April 28, 1987; U.S. Patent 4,987,150 to Kurono et al., issued January 22, 1991; JP 290811 to Ohba et al., published October 15, 1992; JP 05-286,835 to Tanaka et al., published November 2, 1993, FR 2,723,313 to Greff, published August 2, 1994, U. S. Patent 5,015,470 to Gibson, issued May 14, 1991, U.S. Patent 5,559,092, issued September 24, 1996, U.S. Patent 5,536,751, issued July 16, 1996, U.S. Patent 5,714,515, issued February 3, 1998, EPA 0,319,991, published June 14, 1989, EPA 0,357,630, published October 6, 1988, EPA 0,573,253, published December 8, 1993, JP 61-260010, published November 18, 1986, U.S. Patent 5,772,990, issued June 30, 1998, U.S. Patent 5,053, 410, issued October 1, 1991, and U.S. Patent 4,761,401, issued August 2, 1988, all of which are herein incorporated by reference.

Non-limiting examples of penetration enhancers which may be used in the compositions herein include, for example, 2-methyl propan-2-ol, propan-2-ol, ethyl-2-hydroxypropanoate, hexan-2,5-diol, POE(2) ethyl ether, di(2-hydroxypropyl) ether, pentan-2,4-diol, acetone, POE(2)

methyl ether, 2-hydroxypropionic acid, 2-hydroxyoctanoic acid, propan-1-ol, 1,4-dioxane, tetrahydrofuran, butan-1,4-diol, propylene glycol dipelargonate, polyoxypropylene 15 stearyl ether, octyl alcohol, POE ester of oleyl alcohol, oleyl alcohol, lauryl alcohol, dioctyl adipate, dicapryl adipate, di-isopropyl adipate, di-isopropyl sebacate, dibutyl sebacate, diethyl sebacate, dimethyl sebacate, dioctyl sebacate, dibutyl suberate, dioctyl azelate, dibenzyl sebacate, dibutyl phthalate, dibutyl azelate, ethyl myristate, dimethyl azelate, butyl myristate, dibutyl succinate, didecyl phthalate, decyl oleate, ethyl caproate, ethyl salicylate, *iso*-propyl palmitate, ethyl laurate, 2-ethyl-hexyl pelargonate, *iso*-propyl isostearate, butyl laurate, benzyl benzoate, butyl benzoate, hexyl laurate, ethyl caprate, ethyl caprylate, butyl stearate, benzyl salicylate, 2-hydroxypropanoic acid, 2-hyroxyoctanoic acid, dimethyl sulphoxide, N,N-dimethyl acetamide, N,N-dimethyl formamide, 2-pyrrolidone, 1-methyl-2-pyrrolidone, 5-methyl-2-pyrrolidone, 1,5-dimethyl-2-pyrrolidone, 1-ethyl-2-pyrrolidone, phosphine oxides, sugar esters, tetrahydrofurfural alcohol, urea, diethyl-*m*-toluamide, and, 1-dodecylazacycloheptan-2-one.

In all of the foregoing, of course, the compounds used in the present method can be administered alone or as mixtures, and the compositions may further include additional drugs or excipients as appropriate for the indication.

Examples of Composition Administration

The following examples do not limit the invention, but provide guidance to the skilled artisan to perform the methods of the present invention. In each example, a "compound" other than the one mentioned may be substituted in the example by one having a structure as described herein with similar results.

Example A

A composition for topical administration is made, comprising:

Component	Amount
Compound of Example 3	5 %
Ethanol	57 %
Propylene Glycol	19 %
Dimethyl Isosorbide	19 %

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 6 weeks, the above composition is daily administered topically to the subject.

Example B

A composition for topical administration is made according to the method of Dowton et al., "Influence of Liposomal Composition on Topical Delivery of Encapsulated Cyclosporin A: I. An *in vitro* Study Using Hairless Mouse Skin", S.T.P. Pharma Sciences, Vol. 3, pp. 404 - 407 (1993), using the compound of Example 2 in lieu of cyclosporin A and using the Novasome 1 for the non-ionic liposomal formulation.

A human male subject suffering from male pattern baldness is treated each day with the above composition. Specifically, for 6 weeks, the above composition is administered topically to the subject.

Example C

A shampoo is made, comprising:

Component	Ex. C-1	Ex. C-2	Ex. C-3	Ex. C-4
Ammonium Lauryl Sulfate	11.5 %	11.5 %	9.5 %	7.5 %
Ammonium Laureth Sulfate	4 %	3 %	2 %	2 %
Cocamide MEA	2 %	2 %	2 %	2 %
Ethylene Glycol Distearate	2 %	2 %	2 %	2 %
Cetyl Alcohol	2 %	2 %	2 %	2 %
Stearyl Alcohol	1.2 %	1.2 %	1.2 %	1.2 %
Glycerin	1 %	1 %	1 %	1 %
Polyquaternium 10	0.5 %	0.25 %	-	-
Polyquaternium 24	-	-	0.5 %	0.25 %
Sodium Chloride	0.1 %	0.1 %	0.1 %	0.1 %
Sucrose Polyesters of Cottonate Fatty Acid	3 %	3 %	-	-
Sucrose Polyesters of Behenate Fatty Acid	2 %	3 %	-	-
Polydimethyl Siloxane	-	-	3 %	2 %
Cocaminopropyl Betaine	-	1 %	3 %	3 %
Lauryl Dimethyl Amine Oxide	1.5 %	1.5 %	1.5 %	1.5 %
Decyl Polyglucose	-	-	1 %	1 %
DMDM Hydantoin	0.15 %	0.15 %	0.15 %	0.15 %
Compound of Example 5	2 %	-	-	-
Compound of Example 1	-	5 %	-	-
Compound of Example 7	-	-	3 %	-
Compound of Example 8	-	-	-	6 %

Phenoxyethanol	0.5 %	0.5 %	0.5 %	0.5 %
Fragrance	0.5 %	0.5 %	0.5 %	0.5 %
Water	q.s.	q.s.	q.s.	q.s.

A human male subject suffering from male pattern baldness is treated by a method of this invention. Specifically, for 12 weeks, the above shampoo is used daily by the subject.

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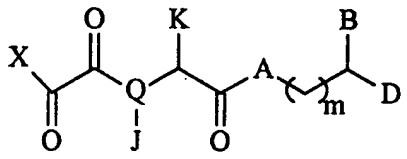
What is claimed is:

1. A method of treating hair loss characterized by administering a composition comprising:

(a) a non-immunosuppressive compound having a structure:



and pharmaceutically acceptable salts, hydrates, and biohydrolyzable amides, esters, and imides thereof, wherein:

(i) Q is a first heteroatom, wherein the first heteroatom is nitrogen;

(ii) A is selected from the group consisting of CH_2, O, S, and NR_1;

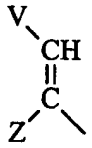
(iii) R_1 is selected from the group consisting of hydrogen and alkyl;

(iv) J is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 alkenyl, benzyl, Ar substituted C_1 - C_6 alkyl, Ar substituted C_3 - C_6 alkenyl, Ar substituted C_3 - C_6 alkynyl; K is selected from the group consisting of C_1 - C_6 alkyl, Ar substituted C_1 - C_6 alkyl, Ar substituted C_2 - C_6 alkenyl, Ar substituted C_2 - C_6 alkynyl, and cyclohexylmethyl; or J and K may be bonded together to form a 5-, 6-, or 7-membered heterocyclic ring wherein the ring may optionally contain an additional heteroatom selected from the group consisting of O, S, S(O), $S(O)_2$, NH, and NE, wherein when B and D are bonded together to form a substituted or unsubstituted tetrahydronapthalene moiety, J and K may be optionally bonded together to form a 5- or 6-membered carbocyclic ring which is fused to a phenyl ring;

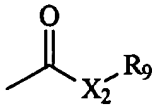
(v) X is selected from the group consisting of hydrogen, C_1 - C_9 alkyl, C_2 - C_9 alkenyl, C_5 - C_7 cycloalkyl, C_5 - C_7 cycloalkyl, C_5 - C_7 cycloalkenyl, C_5 - C_7 cycloalkenyl, Ar, $-OR_2$, [C_1 - C_4 alkyl]-Y, [C_2 - C_4 alkenyl]-Y, Y, and $-NR_3R_4$;

(vi) R_2, R_3, R_4, B, D, and E are each, independently, selected from the group consisting of nil, hydrogen, Ar, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_5 - C_7 cycloalkyl substituted C_1 - C_6 alkyl, C_5 - C_7 cycloalkyl substituted C_3

- C_6 alkenyl, C_5 - C_7 cycloalkyl substituted C_3 - C_6 alkynyl, C_5 - C_7 cycloalkenyl substituted C_1 - C_6 alkyl, C_5 - C_7 cycloalkenyl substituted C_3 - C_6 alkenyl, C_5 - C_7 cycloalkenyl substituted C_3 - C_6 alkynyl, Ar substituted C_1 - C_6 alkyl, Ar substituted C_3 - C_6 alkenyl, and Ar substituted C_3 - C_6 alkynyl; wherein one or more CH_2 moieties of the alkyls, alkenyls, and alkynyls may be optionally replaced by a heteroatom selected from the group consisting of O, S, S(O), $S(O)_2$, and NR, wherein R is selected from the group consisting of hydrogen, C_1 - C_4 alkyl, C_3 - C_4 alkenyl, C_3 - C_4 alkynyl, and C_1 - C_4 bridging alkyl wherein a bridge is formed between the N of NR and a carbon atom of the heteroatom-containing alkyl, alkenyl, or alkynyl to form a bridging ring, and wherein the bridging ring is optionally fused to an Ar moiety; wherein B and D may also be bonded together to form a 5-, 6-, or 7-membered carbocyclic ring which is optionally fused with an aryl; wherein B and D may also be each, independently:



wherein Z is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, and C_2 - C_6 alkynyl, and V is selected from the group consisting of Ar and substituted 5-, 6-, or 7-membered carbocyclic ring having substituents which are independently selected from the group consisting of oxo, hydrogen, hydroxyl, O-(C_1 - C_4 alkyl), and O-(C_2 - C_4 alkenyl); wherein B may also be T, wherein T has the structure:



wherein X_2 is selected from the group consisting of O and NR_{10}, wherein R_{10} is selected from the group consisting of hydrogen, C_1 - C_6 alkyl, and C_1 - C_6 alkenyl; and R_9 is selected from the group consisting of phenyl, benzyl, C_1 - C_5 alkyl, C_1 - C_5 alkenyl, C_1 - C_5 alkyl substituted with phenyl, and C_1 - C_5 alkenyl substituted with phenyl; wherein when B is T, then D is R_8, wherein R_8 is selected from the group consisting of C_1 - C_8 alkyl optionally substituted with C_3 - C_8 cycloalkyl, and Ar; and wherein R_3 and R_4 may also

be bonded together to form a 5-, 6-, or 7-membered heterocyclic aliphatic or aromatic ring;

(vii)Ar and Y are each, independently, selected from the group consisting of phenyl, benzyl, 1-napthyl, 2-napthyl, indenyl, azulenyl, fluorenyl, anthracenyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, 2-pyrazolinyl, pyrazolidinyl, isoxazolyl, isotriazolyl, 1,2,3-oxadiazolyl, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, 1,3,5-trithianyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, benzthiazolyl, purinyl, 4H-quinolizinyl, quinolinyl, 1,2,3,4-tetrahydroquinolinyl, isoquinolinyl, 1,2,3,4,-tetrahydroisoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 1,8-napthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, and phenoxazinyl, 2-pyrrolinyl, 3-pyrrolinyl, pyrolidinyl, 1,3-dioxolyl, imidazolidinyl, 2H-pyranyl, 4H-pyranyl, piperidyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl, piperazinyl, and quinuclidinyl; wherein Ar bears one or more substituents independently selected from the group consisting of hydrogen, halogen, hydroxyl, nitro, $-SO_3H$, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, O-[C_1 - C_6 alkyl], O-[C_2 - C_4 alkenyl], O-benzyl, O-phenyl, 1,2,-methylenedioxy, $-NR_5R_6$, carboxyl, N-[C_1 - C_5 alkyl] carboxamide, N-[C_3 - C_5 alkenyl] carboxamide, N,N-di-[C_1 - C_5 alkyl] carboxamide, N,N-di-[C_3 - C_5 alkenyl] carboxamide, N-morpholinocarboxamide, N-benzylcarboxamide, N-thiomorpholinocarboxamide, N-picolinoylcarboxamide, morpholinyl, piperidinyl, O-M, CH_2-$(CH_2)_q$-M, O-$(CH_2)_q$-M, $(CH_2)_q$-O-M, and CH=CH-M; wherein R_5 and R_6 are each, independently, selected from the group consisting of hydrogen, C_1 - C_6 alkyl, C_3 - C_6 alkenyl, C_3 - C_6 alkynyl, and benzyl, or R_5 and R_6 may be bonded together to form a 5- or 6-membered heterocyclic ring; M is selected from the group consisting of 4-methoxyphenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrazyl, quinolyl, 3,5-dimethylisoxazoyl, isoxazoyl, 2-methylthiazoyl, thiazoyl, 2-thienyl, 3-thienyl, and pyrimidyl; and q is an integer from 0 to 2; and wherein Y bears one or more substituents independently selected from the group consisting of

hydrogen, halogen, hydroxyl, nitro, trifluoromethyl, trifluoromethoxy, C_1 - C_6 alkyl, C_1 - C_6 alkenyl, O-[C_1 - C_4 alkyl], O-[C_2 - C_4 alkenyl], O-benzyl, O-phenyl, 1,2-methylenedioxy, amino, and carboxyl; and

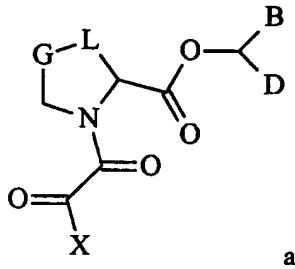
(viii) m is an integer from 0 to 3; and

(b) a pharmaceutically-acceptable carrier.

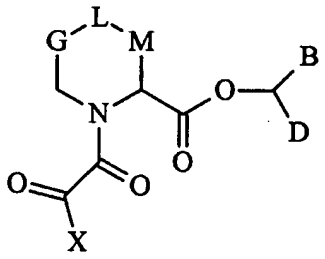
2. A method according to Claim 1 wherein J and K are bonded together to form the 5-, 6-, or 7-membered heterocyclic ring and m is and integer from 0 to 1.

3. A method according to any of the preceding claims wherein J and K are bonded together to form a 5-, 6-, or 7-membered heterocyclic ring which contains an additional heteroatom selected from the group consisting of S, O, NH, and NE.

4. A method according to any of Claims 1 or 2 wherein the compound has a structure selected from the group consisting of:

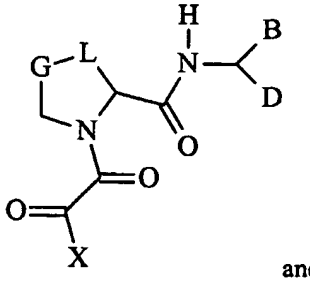


and

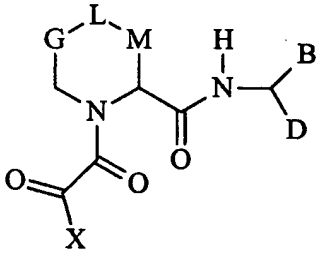


wherein G, L, and M are each, independently, selected from the group consisting of CH_2, S, O, NH, and NE.

5. A method according to any of Claims 1 or 2 wherein the compound has a structure selected from the group consisting of:

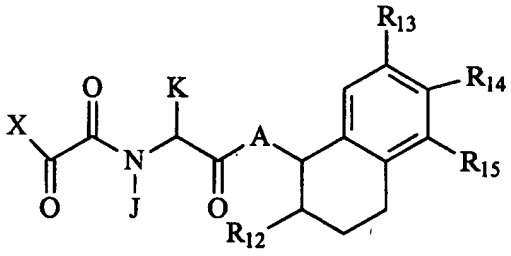


and



wherein G, L, and M are each, independently, selected from the group consisting of CH_2, S, O, NH, and NE.

6. A method according to any of Claims 1 or 2 wherein the compound has the structure:



wherein:

(a) R_{12} is selected from the group consisting of hydrogen and $-(CH_2)_t-R_{16}$, wherein t is an integer from 1 to 3 and R_{16} is selected from the group consisting of Ar and $NR_{17}R_{18}$, wherein R_{17} and R_{18} are each, independently, selected from the group consisting of hydrogen, C_1 - C_5 alkyl, and $-(CH_2)$-Ar, or R_{17} and R_{18} may be bonded together to form a 5- or 6-membered heterocyclic ring;

(b) R_{13}, R_{14}, and R_{15} are each, independently, selected from the group consisting of hydrogen, halogen, C_1 - C_6 alkyl, O-(C_1 - C_6 alkyl), $-(CH_2)_e$-Ar, and $-G(CH_2)_e$-Ar, wherein e is an integer from 0 to 4; and G is selected from the group consisting of O, S, and NR_{19}, wherein R_{19} is selected from the group consisting of hydrogen and C_1 - C_6 alkyl; and

(c) A is selected from the group consisting of -O- and -NH-.

7. A method according to Claim 6 wherein:

(a) R_{13} are R_{15} are each, independently, selected from the group consisting of $-OCH_2$-4-pyridine, -O-propyl, and hydrogen;

(b) R_{14} is selected from the group consisting of $-OCH_2$-4-pyridine, methyl, and hydrogen;

(c) R_{12} is selected from the group consisting of $-CH_2$-3-pyridine and hydrogen;

(d) A is selected from the group consisting of O, NH_2, and N-benzyl; and

(e) X is 3,4,5-trimethoxyphenyl.

8. A method according to Claim 7 wherein:

(a) R_{13} are R_{15} are each, independently, selected from the group consisting of $-OCH_2$-4-pyridine, -O-propyl, and hydrogen;

(b) R_{14} is selected from the group consisting of -OCH_2-4-pyridine, methyl, and hydrogen;

(c) R_{12} is selected from the group consisting of -CH_2-3-pyridine and hydrogen;

(d) A is selected from the group consisting of O, NH_2, and N-benzyl; and

(e) X is 3,4,5-trimethoxyphenyl.

9. A method according to any of the preceding claims wherein the administration is topical.

10. A method according to any of the preceding claims wherein the administration is oral.